EXAMINING ASSOCIATIONS BETWEEN SPECIFIC PHYSICAL ACTIVITY VARIABLES AND CANCER INCIDENCE

by

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ABSTRACT

Cancer is the second leading cause of death in the United States, resulting in the deaths of an estimated 600,000 people in 2016. Yet, about 50% of all cancers are thought to be preventable, through increased screenings, and environmental and behavioral modifications. Research around the role of physical activity in the prevention of cancer has been expanding over the last 10 years, demonstrating convincing evidence that physical activity does reduce the risk for many cancers, including breast, colorectal, lung, endometrial, and others. Yet, some questions remain around the specific attributes of physical activity, such as the type, frequency, intensity, and duration needed to improve cancer risk. The purpose of the following research was to explore these attributes of physical activity and subsequent cancer incidence among the Prostate, Lung, Colorectal, and Ovarian cancer screening trial cohort.

To Brandy Durk, who is eagerly awaiting the free meals that have been promised upon receipt of this degree and to my dear Marcos, who has always ensured I never sit for too long.

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CHAPTER 1

INTRODUCTION

Overview

In 2016, about 600,000 Americans are expected to die from cancer.[1] 1.6 million Americans will be diagnosed with cancer in the same timeframe.[1] Cancer is the second leading cause of death in the United States, behind heart disease (Cancer Facts & Figures 2016; AICR).[1,2] Fortunately, cancer deaths are dropping, due to a combination of public health prevention measures, and improvement in detection and treatment.[1] In his State of the Union address, President Obama declared a new cancer initiative – a "moonshot" to continue to improve prevention, early detection, and treatment of cancers.[3] With more money, effort, and visibility around cancer than at any other time in history, we are currently poised to make more rapid and transformative improvements than ever before.

A large portion of the effort to address cancer must come through prevention. Up to 50% of cancer deaths are thought to be preventable through reducing unhealthy behaviors, such as smoking, and through improving existing behaviors, like increasing the nutritional quality of the American diet.[2] For individuals with a family history of cancer, their increased risk is thought to be a result of interplay between genetic, environmental, and behavioral factors, suggesting that preventive behaviors have something to offer them too.

Physical activity is one of the preventive behaviors that has received increased attention in the past 20 years, with increasing evidence showing that it plays a role in reducing the risk of certain cancers. A systematic review by Friedenreich et al.[4] found convincing evidence, based on the number of studies conducted, the strength of identified associations in the literature, and the consistency of the findings, that physical activity reduces the risk for colon, breast, and endometrial cancer and possibly reduces the risk for lung, prostate, and ovarian cancers.[4] A similar review by Kruk and Czerniak[5], found strong evidence for physical activity to reduce risk of colorectal cancer, postmenopausal breast cancer, and endometrial cancer, with probable reductions for premenopausal breast cancer, prostate, lung, ovarian, pancreatic, and gastric cancers.

Recently, more evidence is accumulating for the role of physical activity in preventing other cancer types as well. A recent pooled analysis of more than 1.4 million participants from 12 different prospective cohorts (including the Prostate, Lung, Colorectal and Ovarian Cancer Screening trial, which is the data source for the current study) in the United States and Europe found that, compared to those who did little or no physical activity, individuals who engaged in high levels of leisure time physical activity had reduced risk of 13 different cancers, including esophageal (HR: 0.58, 95% CI: 0.37, 0.89), liver (HR: 0.73, 95% CI: 0.55-0.98), lung (HR: 0.74, 95% CI: 0.71-0.77), kidney (HR: 0.77, 95% CI: 0.70, 0.88), gastric cardia (HR: 0.78, 95% CI: 0.64-0.95), endometrial (HR: 0.79, 95% CI: 0.68-0.92), myeloid leukemia (HR: 0.80, 95% CI: 0.70-0.92), colon (HR: 0.84, 95% CI: 0.77-0.91), head and neck (HR: 0.85, 95% CI: 0.78-0.93), rectal (HR: 0.87, 95% CI: 0.80- 0.95), bladder (HR: 0.87, 95% CI: 0.82-0.92), and breast (HR: 0.90, 95% CI: 0.87-0.93).[6] This study represents one of the largest pooled analyses on the relationship between physical activity and cancer prevention to date.

Although physical activity was primarily associated with reduced risk for cancer, the study also found that physical activity increased the risk for some cancers, including malignant melanoma (HR: 1.27, 95% CI: 1.16-1.40) and prostate cancer (HR: 1.05, 95% CI: 1.03-1.08).[6] Further, when the analyses were adjusted for BMI, three of the reduced risk associations (liver, endometrial, gastric) were no longer significant.[6] Eight of the 26 hazard rates changed by 5% or more after BMI adjustment, suggesting that the role of obesity, physical activity, and cancer is heavily influenced by body weight, depending on the type of cancer.[6] These findings suggest that, while physical activity does appear to play a role in preventing many cancers, the relationship may be strongly influenced by factors such as cancer site and adiposity.

Biomechanisms of Physical Activity in Preventing Cancer

There are various hypotheses regarding the biomechanisms by which physical activity reduces cancer risk.

Reduction of Adiposity

Obesity has been linked to several cancers, including endometrial, esophageal, colorectal, postmenopausal breast, prostate, and renal cancers.[7] The biomechanisms governing obesity include attributes that are separately linked to increased cancer risk, including insulin disruption, increased levels of sex hormones, heightened bioavailability of insulin-like growth factor, and inflammation.[8] The combination of these bio-attributes of obesity may explain why obesity, even more than sedentary behavior, is so closely linked to increased cancer risk.[9] The role of obesity, physical activity, and cancer outcomes is complex. Physical activity throughout the life course has been found to protect against encroaching weight gain, which has been associated with an increased risk of certain cancers, such as colorectal cancer.[10, 11, 12] Yet, obesity is influenced not simply by lifestyle choices, but also environmental, genetic, and medical factors that may not be responsive to simple dietary and physical activity modifications.[11,12] Obese individuals may engage in lower levels of physical activity than normal weight individuals,[13] but their inactivity may be the result of obesity, rather than obesity as a result of their inactivity. Thus, how to assess and interpret the effect modification of obesity is an important aspect of studying the relationship between physical activity and cancer. Many studies have simply adjusted for BMI, while others have disaggregated findings by BMI category, and still others[6] have conducted analyses with and without adjustments for comparison.

Regulation of Sex Hormones

Physical activity helps to regulate androgens, estrogen, testosterone, and sex-hormone binding globlulin (SHBG).[14] Increased estrogen is associated with an increased risk for breast and endometrial cancers, while free androgens have been associated with prostate cancer risk.[9] Prospective trials measuring the effect of physical activity on sex hormone concentrations found that physical activity decreased the amount of free estradiol and estrone, while increasing levels of SHBG.[14]

Improvement of Blood Glucose

Physical activity helps regulate metabolic hormones, including insulin and insulin-like growth factor (IGF-I), which have been associated with increased risk for cancers, through mitogenic and anti-apoptotic mechanisms. A systematic review of clinical trials studying biomechanisms affected by physical activity found evidence from some studies that increased physical activity did decrease insulin resistance and reduce serum insulin levels.[14] A study by Dube et al.[15] found that increased frequency of aerobic physical activity resulted in dose-response improvements to insulin sensitivity, suggesting that specific attributes of physical activity, such as activity type and frequency, may be important in blood glucose regulation and function.

Reduction of Inflammation

Inflammation is a known risk factor for cancer, as chronic inflammation can lead to cell dysplasia and an increase in pro-inflammatory factors, such as C-reactive protein and interleukin-6.[9,16] Physical activity increases anti-inflammatory proteins, like adiponectin, and decreases pro-inflammatory factors.[14,17]

A Public Health Challenge

Despite the known benefits of physical activity to reduce incidence of cancer and other diseases, including diabetes, mental illness, cardiovascular disease, Alzheimer's disease, and others, only a small percentage of the population engages in recommended levels of physical activity.[18,19] According to the Centers for Disease Control, only one in five adults meet the recommended guidelines for physical activity.[20] Levels of physical activity in older adults, who are the primary cancer population, are even lower. One study of older adults (>60 years) in the United States found that only 8.5% of adults ages 60-69 met recommended physical activity guidelines, and only 6.3% of adults over age 70 did.[21] Older women, in particular, are less likely to obtain recommended levels of physical activity than men.[22]

Unfortunately, sedentary behaviors can be reinforcing – individuals who are less physically active report insecurity, low fitness levels, and body image dissatisfaction as major reasons for remaining inactive.[23] One major factor for behavioral adherence to physical activity (and other health behaviors) is improved self-efficacy around a behavior.[24] Individuals who have confidence in their ability to be physically active in specific situations are more likely to continuously engage in physical activity.[24] However, mechanisms enhancing self-efficacy to improve physical adherence in older populations do not necessarily mirror successful interventions in the general population. A systematic review by French et al.[25] found that many traditionally validated aspects of increasing self-efficacy, such as obtaining feedback on performance or developing a plan to act, do not increase self-efficacy within older adult populations, with regard to physical activity. Instead, older adults appear to place more prioritization on maximizing meaning and positive emotions, with less regard for future effects, such as health.[25]

Simply put, there is potentially a great benefit to identifying the minimal effective dose of physical activity necessary to achieve cancer risk reduction for older adults. This information can then be included in programs designed to increase physical activity among older individuals, along with mechanisms that most successfully effect behavioral change, such as the findings related to self-efficacy in this population.[25] As the field of preventive cancer research establishes more evidence of the important role of physical activity in reducing cancer risk, there is an increasing need to also identify which specific attributes of physical activity contribute to this reduction. Specificity is a natural progression of increased epidemiologic study, and allows public-health practitioners and health care providers to translate scientific evidence into real-world recommendations.[26] Yet, thus far, the accumulated evidence around physical activity and cancer prevention has relatively low specificity, with respect to the type, intensity, duration, and frequency of physical activity necessary to affect risk.

This is due, in part, to lack of consistency in the measurement of physical activity. Longitudinal studies that assessed cancer incidence over time often did not adequately assess physical activity at initial outset, as the connection between exercise and cancer is a more recent development in cancer research. As such, measures of physical activity often are generalized, for example, to constructs such as weekly time spent in "leisure activity." Physical activity measurements, in general, have become more standardized in the last 10 years.[27] As the metrics improve, doubtless more specific information will also emerge, regarding which attributes of physical activity affect cancer risk.

The purpose of the research presented here is to explore aspects of existing questions around the role of physical activity and cancer. We identified participants who were enrolled in a large, prospective efficacy trial that contained relatively specific attributes of physical activity, including activity type (aerobic/strength-based), frequency (per week), intensity (moderate/vigorous), and average duration of each activity session (in minutes). Our analyses evaluate these variables with respect to cancer outcomes broadly (for all cancers), for specific cancer types, and for individuals with a family history of cancer.

References

1. American Cancer Society. Cancer Facts & Figures 2016. Atlanta: American Cancer Society; 2016.

2. American Association for Cancer Research. AACR Cancer Progress Report 2014. *Clin Cancer Res*. 2014;20(Supplement 1):S1-S11.

3. The White House. Remarks of President Barack Obama – State of the Union Address As Delivered January 13, 2016.

4. Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. *Euro J Cancer*. 2010;46:2593-2604. doi:10.1016/j.ejca.2010.07.028.

5. Kruk J, Czerniak U. Physical activity and its relation to cancer risk: updating the evidence. *Asian Pac J Cancer Prev*. 2013;14(7):3993-4003. doi:10.7314/APJCP.2013.14.7.3993.

6. Moore SC, Lee I, Weiderpass E, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA Intern Med*. 2016;176(6):816-825. doi:10.1001/jamainternmed.2016.1548.

7. De Pergola G, Silvestris F. Obesity as a major risk factor for cancer. *J Obes*. 2013. doi:10.1155/2013/291546.

8. Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. *Nature*. 2015;15:484-498. doi:10.1038/nrc3967.

9. McTiernan A. Mechanisms linking physical activity with cancer. *Nat Rev*. 2008;8:205-211. doi:10.1038/nrc2325.

10. Karahalios A, English DR, Simpson JA. Weight change and risk of colorectal cancer: a systematic review and meta-analysis. *Am J Epidemiol*. 2015;181(11). doi:10.1093/aje/kwu357.

11. Locke AE, Kahali B, Berndt S, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature*. 2015;518:197. doi:10.1038/nature14177.

12. Pate RR, O'Neill JR, Liese KF, et al. Factors associated with development of excessive fatness in children and adolescents: a review of prospective studies. *Obes Rev*. 2013;14(8):645-658. doi:10.1111/obr.12035.

13. Adams SA, Der Ananian CA, DuBose KD, Kirtland KA, Ainsworth BE. Physical activity levels among overweight and obese adults in South Carolina. *South Med J*. 2003;96(6):539-543.

14. Winzer BM, Whiteman DC, Reeves MM, Paratz JD. Physical activity and cancer prevention: a systematic review of clinical trials. *Cancer Causes Control*. 2011;22:811-826. doi:10.1007/s10552-011-9761-4.

15. Dube JJ, Fleishman K, Rousson V, Goodpaster BH, Amati F. Exercise dose and insulin sensitivity: relevance for diabetes prevention. *Med Sci Sports Exerc*. 2012;44(5):793-799. doi:10.1249/MSS.0b013e31823f679f.

16. Rakoff-Nahoum S. Why cancer and inflammation? *Yale J Biol Med*. 2006;79:123-130.

17. Simpson KA, Singh F. Effects of exercise on adiponectin: a systematic review. *Obesity*. 2008;16:241-256. doi:10.1038/oby.2007.53.

18. Elwood P, Galante J, Pickering J, et al. Healthy lifestyles reduce the incidence of chronic diseases and dementia: evidence from the Caerphilly Cohort Study. *PLoS ONE*. 2013;8(12):e81877. doi:10.1371/journal.pone.0081877.

19. Nunan D, Mahtani KR, Roberts N, Heneghan C. Physical activity for the prevention and treatment of major chronic disease: an overview of systematic reviews. *Syst Rev*. 2013;2:56. doi:10.1186/2046-4053-2-56.

20. Centers for Disease Control and Prevention. Press Release: One in five adults meet overall physical activity guidelines 2013. https://www.cdc.gov/media/releases/2013/p0502-physical-activity.html. Accessed September 4, 2016.

21. Tucker JM, Welk GJ, Beyler NK. Physical activity in U.S. adults. Compliance with the Physical Activity Guidelines for Americans. *Am J Prev Med*. 2011;40(4):454-461. doi:10.1016/j.amepre.2010.12.016.

22. Sun F, Norman IJ, While AE. Physical activity in older people: a systematic review. *BMC Public Health*. 2013;13:449. doi:10.1186/1471-2458-13-449.

23. Grave RD, Calugi S, Centis E, El Ghoch M, Marchesini G. Cognitive-behavioral strategies to increase the adherence to exercise in the management of obesity. *J Obes*. 2011. doi:10.1155/2011/348293.

24. Bauman AE, Reis RS, Sallis JF, Wells JC, Loos RJF, Martin BW. Correlates of physical activity: why are some people physically active and others not? *Lancet*. 2012;380:258-71. doi:10.1016/S0140-6736(12)60735-1.

25. French DP, Olander EK, Chisholm A, McSharry J. Which behavior change techniques are most effective at increasing older adults' self-efficacy and physical activity behavior? A systematic review. *Ann Behav Med*. 2014;48:225-234. doi:10.1007/s12160-014-9593-z.

26. Curry SJ, Grossman DC, Whitlock EP, Cantu A. Behavioral counseling research and evidence-based practice recommendations: U.S. Preventive Service Task Force perspectives. *Ann Intern Med*. 2014;160:407-413.

27. Warren JM, Ekelund U, Besson H, Mezzani A, Gelados N, Vanhees L. Assessment of physical activity – a review of methodologies with reference to epidemiological research: a report of the exercise physiology section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil*. 2010;17:127-139. doi:10.1097/HJR.0b013e32832ed875.

CHAPTER 2

EXPLORING THE RELATIONSHIP BETWEEN SPECIFIC PHYSICAL ACTIVITY ATTRIBUTES AND ALL-CANCER INCIDENCE

Abstract

Physical activity reduces the risk of some cancers, including breast, colorectal, and endometrial cancer. Yet, more information is needed on the specific types, intensity, and duration of activity necessary to decrease cancer risk. This secondary analysis utilized data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial cohort (n= 75,623) from 1993-2013. We examined associations between variables of activity type, duration, intensity, and existing physical activity recommendations with all-cancer incidence using multivariate Cox proportional hazards models stratified by Body Mass Index (BMI) categories. No associations between physical activity and all-cancer incidence were found in normal or overweight men and women. However, increased aerobic activity was found to be significantly protective against all-cancer incidence in obese women (HR: 0.85; 95% CI: 0.77, 0.94). Additionally, increased total frequency of any activity type in obese women was also protective against all-cancer incidence (HR: 0.91; 95% CI: 0.86, 0.97). No associations between current recommended physical activity guidelines and all-cancer incidence were identified. Obese women performing aerobic activities regularly were less likely to be diagnosed with any type of

cancer. These findings lend support to public health programs aimed at improving physical activity as part of a cancer prevention strategy.

Introduction

Physical activity has been associated with cancer-related benefits and reduced risk for certain types of cancer, such as breast, colorectal, and endometrial cancers.[1,2] For individuals with cancer, physical activity both before and after diagnosis has been shown to improve response to treatment and increase chance of survival.[3] For survivors of cancer, physical activity has been shown to improve quality of life and reduce cancer-related comorbidities.[4] Movement, in essence, is one of the most powerful means we have to improve cancer-related outcomes at all levels of prevention.

Several theories have been posed about the biological mechanisms at work during physical activity that confer these benefits. Physical activity improves production of sex hormone binding globulin, which can improve the balance of bioavailable sex hormones, including estrogen and testosterone.[5] Physical activity also helps to regulate insulin levels and decreases levels of insulin-like growth factor, of which high levels have been implicated in breast, colorectal, and prostate cancers.[1,5-6] Finally, an estimated 25% of cancers are associated with chronic inflammation.[7] Previous studies have demonstrated that physical activity plays a key role in decreasing inflammatory response.[8]

In particular, physical activity appears to play a mitigating role in biological mechanisms involved in cancer risk for individuals who are overweight or obese. Obesity has been associated with an increased risk for several cancers, including breast, colorectal, pancreatic, kidney, and esophageal cancers[1,9] and some evidence suggests that physical activity may help to mitigate cancer risks in those who are overweight. Michaud et al.[10] found that physical activity reduced the risk of pancreatic cancer in individuals who were overweight or obese, but did not affect risk for individuals who were of normal weight. Similarly, while obesity is strongly associated with breast cancer risk, Pierce et al. found that physical activity, combined with fruit and vegetable intake, improved breast cancer survival similarly in both obese and non-obese individuals.[11] Given that obesity is independently related to increased insulin-like-growth factor and estrogenic imbalances, it is perhaps unsurprising that physical activity would be particularly beneficial in improving cancer risk in these individuals.[12,13]

Although a strong body of evidence is emerging on the benefits of physical activity with regard to cancer, many questions remain regarding the relationship between physical activity and cancer incidence, such as the type, frequency, duration, and intensity of physical activity that decrease cancer risk. The most robust research in this area focuses on both breast and colorectal cancer prevention and has shown that, in general, 30-60 minutes per day of moderate-to-strenuous activity reduces risk of developing these cancers.[14] Some studies have found that leisure activities are associated with decreased risk for certain cancers, while other studies have found that occupational activity is protective.[2,15]

To our knowledge, no study has assessed the effects of physical activity on all-cancer incidence. Cancer is generally assessed by cancer type, as the etiology and risk factors for different cancers vary. Indeed, cancer is not one specific disease, but rather a series of diseases under a single label. However, despite differences between cancer types, the term ‘cancer’ is frequently discussed in aggregate in public health discourse, and cancer outcomes, such as mortality, are regularly grouped together in public health research. Thus, the purpose of this paper is to identify whether there are any overarching associations between physical activity and cancer that transcend cancer type; such findings could yield broader public health recommendations around physical activity as it relates to cancer prevention. The current study sought to determine how physical activity type, frequency, duration, and intensity, as well as whether adherence to current public health recommendations for physical activity, affect all-cancer incidence in a large, multi-state cancer trial.

Method

Participants

Participants were men and women who participated in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), a randomized controlled trial of the effect on mortality of screening for these four cancers. Participants were originally enrolled in the trial between 1993 and 2001 and were followed for at least 13 years. Detailed recruitment and enrollment strategies were published previously.[16] Baseline demographic, personal and family history data, as well as a dietary history questionnaire and limited physical activity data were collected from participants at initiation. In 2006, a supplemental questionnaire (SQX) was introduced, with additional questions about physical activity, including types of physical activity engaged in per week and weekly frequency of activity and activity intensity (strenuous, moderate, and light). Annual data collection was completed in 2009[17]; however, limited data collection is still ongoing.

Between 1993 and 2001, the PLCO trial enrolled 154,898 men and women, ages 55-74 years. The subset included in this study met the following criteria: 1) complete baseline and dietary history information; 2) completed the SQX questionnaire; 3) did not have a diagnosis of cancer at the time of SQX data collection; and 4) had follow-up data up through year 13 of study enrollment (2013). Of those enrolled, 149,978 completed baseline information, and 101,950 completed SQX information. Regarding those who had completed the SQX information, 100,704 responded to the physical activity questions and 85,430 had never been diagnosed with cancer by the time they completed the SQX questionnaire. Of those, 78,687 (36,969 men and 41,718 women) had follow-up information through 2013.

Statistical Analyses

We separated men and women for the analyses, as certain confounding variables, such as hormone-replacement therapy status, were sex-specific. We then stratified on BMI to account for the potentially different biological mechanisms involved between obesity and cancer risk. As very few individuals with a BMI of under 18.5 were diagnosed with cancer (13 females and 11 males), we combined the underweight individuals with individuals in the normal weight category for the final analyses.

Using the physical activity variables obtained from the SQX questionnaire, we created two composite variables of activity frequency. We first divided reported variables into aerobic and strength type categories. We then created composite variables for total aerobic and total strength activities, by adding all self-reported weekly frequency of specific activities (e.g., 2 times dancing, 2 times jogging, 2 times swimming would equal 6 aerobic activities in one week). We then created a variable for total frequency of all reported activity (strength and aerobic combined).

We were also interested in examining how proportion of time spent in a specific type of activity influenced cancer outcomes. For example, if an individual is highly active, but only does strength training activities (compared to aerobic activities), does it affect their risk differently than an individual who divides time more evenly between activity types? To assess this, we created two ratio variables, which identified the proportion of total activity frequency spent in either type of activity.

We were also interested in exploring variables of intensity and duration. The SQX questionnaire asked questions about weekly frequency of strenuous and moderate activity, as well as questions about the average duration of each strenuous/moderate activity session. Unfortunately, due to the categories created within the SQX for these variables, we were unable to combine them for a more standard measure of total weekly time spent in strenuous or moderate activity. Nonetheless, we analyzed the intensity and duration variables separately in our analyses.

We explored all variables listed in Table 2.1 as potential confounders or covariates in the model and retained all variables that were statistically significant ($p<0.05$) in univariate analyses or were supported by existing literature as associated with cancer incidence. Additionally, we conducted sensitivity analyses to assess the potential effect of extreme physical activity variables.

Hazard ratios and 95% confidence intervals (CIs) were estimated using Cox proportional hazard regression models with all-cancer incidence as the underlying time function. Cancer types in the all-cancer incidence variable included: prostate, lung, colon, ovarian, pancreatic, melanoma, bladder, breast, hematopoietic, endometrial, glioma, renal, thyroid, head and neck, liver, upper GI, and biliary cancers. Follow-up was defined as time after completion of the SQX questionnaire until cancer incidence or the end of follow-up (13 years from enrollment or through 2013, whichever occurred first).

Table 2.1. Demographic Overview of Prostate, Lung, Colorectal (PLCO) Cancer Trial Participants by Cancer Incidence at Follow-Up

	Females		Males	
	Cancer diagnosis at follow-up		Cancer diagnosis at follow-up	
	Yes	No	Yes	No
Average age at randomization	62.1	61.7	61.8	61.7
Race				
Non-white	131 (8.2%)	3,662 (9.5%)	179 (8.1%)	3,008 (9.0%)
White	1,461 (91.8%)	34,700 (90.4%)	2,050 (91.9%)	30,432 (91.0%)
Body mass index [a]				
<18.5	11 (0.7%)	367 (0.9%)	7 (0.3%)	87 (0.3%)
18.5-25	567 (36.1%)	15,594 (41.1%)	577 (26.3%)	8,520 (25.8%)
25-30	584 (37.1%)	13,274 (35.1%)	1,091 (49.7%)	17,001 (51.5%)
30+	411 (26.1%)	8,683 (22.9%)	521 (23.7%)	7,387 (22.4%)
Family History of Cancer				
Yes	1,014 (64.8%)	22,598 (59.1%)	1,195 (53.7%)	17,290 (51.8%)
No	574 (36.2%)	15,636 (40.9%)	1,030 (46.3%)	16,049 (48.1%)
Average daily servings of vegetables	3.85	3.86	3.93	4.02
Average daily servings of fruit	2.71	2.83	2.48	2.63
Average alcoholic drinks per day	0.45	0.41	1.45	1.23
Smoking status				
Never smoked	775 (50.2%)	20,968 (56.4%)	711 (32.5%)	11,791 (36.0%)
Current smoker	135 (8.7%)	2,185 (5.9%)	225 (10.3%)	2,159 (6.6%)
Former smoker	635 (41.1%)	14,004 (37.7%)	1,252 (57.2%)	18,807 (57.4%)
Average smoking pack years	17.52	12.28	29.2	24.2

Following analysis, we applied the Benjamini-Hochberg procedure for multiple test correction with a false discovery rate of 0.10. All analyses were conducted in Stata 12.0. The current study was approved by the University of Utah Institutional Review Board.

Results

There were 3,821 confirmed cancers among participants in the current study (males: 2,229; females: 1,592). Tables 2.2 and 2.3 show findings for adjusted analyses for women and men, stratified by BMI. Highlighted findings identify those variables that maintained significance after multiple test correction. No physical activity variables were implicated in affecting risk of all-cancer incidence in women with BMI below 29; however, for women who had a BMI of 30 or above, higher amounts of weekly physical activity were modestly associated with decreased risk of all cancer incidence. Specifically, aerobic activity frequency (HR: 0.85, 95% CI: 0.77, 0.94) and total activity frequency per week (HR: 0.91, 95% CI: 0.86, 0.97) were found to reduce the risk of all cancer incidence.

After adjusting for multiple test correction, no physical activity variables were associated with a risk of all-cancer incidence in men, across BMI categories.

Discussion

Our findings support physical activity, particularly aerobic physical activity, as a cancer-prevention tool for older obese women. This study is the first that we are aware of that examines the relationship between physical activity and all-cancer incidence. The relatively large amount of physical activity data collected during the trial allowed us to examine variables that, thus far, have not been assessed in the literature, including how the ratio of different activity types may affect cancer outcomes.

Table 2.2. Associations between Self-Reported Physical Activity Variables and All-Cancer Incidence in Female Participants in the Prostate, Lung, Ovarian, and Colorectal Cancer Study Population, Stratified by Body Mass Index (n = 39,954)[a,b,c]

	BMI[b] Under 25		BMI 25-29		BMI 30+	
Type of physical activity	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Total weekly aerobic activity[d] frequency	1.04 (0.98, 1.11)	0.16	1.01 (0.95, 1.08)	0.62	0.85 (0.77, 0.94)	0.002
Total weekly strength training[e] frequency	1.02 (0.96, 1.08)	0.39	1.03 (0.97, 1.10)	0.29	0.94 (0.86, 1.02)	0.18
Total frequency of all activities per month	1.02 (0.98, 1.06)	0.16	1.02 (0.97, 1.06)	0.32	0.91 (0.86, 0.97)	0.004
Ratio of aerobic activity over all activity per month	0.90 (0.60, 1.23)	0.52	1.00 (0.76, 1.33)	0.95	0.67 (0.46, 0.96)	0.03
Ratio of strength training activity over all activity per month	0.96 (0.70, 1.31)	0.81	1.02 (0.76, 1.37)	0.89	1.47 (1.02, 2.12)	0.04
Weekly frequency of strenuous activity						
<2 times per week	Ref		Ref		Ref	
3-4 times per week	1.05 (0.85, 1.32)	0.62	0.94 (0.71, 1.16)	0.57	1.11 (0.87, 1.42)	0.38
5-6 times per week	1.17 (0.85, 1.60)	0.32	1.13 (0.82, 1.56)	0.44	0.71 (0.42, 1.20)	0.20
7+ times per week	1.51 (0.98, 2.33)	0.06	1.10 (0.64, 1.90)	0.70	0.88 (0.39, 1.99)	0.76
Average duration of strenuous activity sessions						
<15 minutes/session	Ref		Ref		Ref	
15-29 minutes/session	0.94 (0.72, 1.22)	0.67	1.02 (0.81, 1.29)	0.81	0.93 (0.70, 1.23)	0.63
30+ minutes/session	1.26 (1.00, 1.57)	0.04	0.87 (0.68, 1.10)	0.25	0.81 (0.60, 1.09)	0.17
Weekly frequency of moderate activity						
<2 times per week	Ref		Ref		Ref	
3-4 times per week	1.04 (0.82, 1.32)	0.70	1.14 (0.91, 1.43)	0.23	0.79 (0.62, 1.01)	0.07
5-6 times per week	0.96 (0.70, 1.30)	0.79	1.33 (1.00, 1.77)	0.05	0.78 (0.53. 1.17)	0.24
7+ times per week	1.21 (0.84, 1.74)	0.30	1.17 (0.75, 1.82)	0.47	1.03 (0.60, 1.75)	0.91
Average duration of moderate activity sessions						
<15 minutes/session	Ref		Ref		Ref	
15-29 minutes/session	0.92 (0.69, 1.21)	0.56	1.11 (0.87, 1.42)	0.39	0.81 (0.62, 1.05)	0.11
30+ minutes/session	1.26 (0.97, 1.62)	0.07	1.13 (0.88, 1.44)	0.31	0.82 (0.62, 1.08)	0.18

[a] Models are adjusted on: age, race (white/non-white), age at first menstruation, age at menarche, number of pregnancies, birth control use (ever/never), family history of cancer (yes/no), number of servings of fruit and vegetables eaten per day, number of alcoholic drinks per day, hormone replacement therapy status (ever/never/former), smoking status (ever/never/former), and smoking pack years.

[b] Body mass index (BMI) was calculated using participant height and weight information collected at the time of the SQX completion.

[c] Hazard ratios and p-values emboldened represent those rates that maintained significance after applying the Benjamini-Hochberg correction procedure with a false discovery rate of 0.10.

[d] Aerobic activities included: aerobics, cycling, dancing, jogging, swimming, and walking one mile without stopping.

[e] Strength training activities included: gardening, weight lifting, and calisthenics. Gardening categorized as a strength based activity according to the National Institutes of Health: https://www.nhlbi.nih.gov/health/health-topics/topics/phys/types

Table 2.3. Associations between Self-Reported Physical Activity Variables and All-Cancer Incidence in Male Participants in the Prostate, Lung, Ovarian, and Colorectal Cancer Study Population, Stratified by Body Mass Index (n = 36,969)[a,b,c]

	BMI[b] Under 25		BMI 25-29		BMI 30+	
Type of physical activity	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Total weekly aerobic activity[d] frequency	1.00 (0.94, 1.07)	0.76	0.98 (0.93, 1.03)	0.56	0.93 (0.86, 1.01)	0.10
Total weekly strength training[e] frequency	0.98 (0.93, 1.04)	0.71	0.97 (0.93, 1.02)	0.33	1.00 (0.94, 1.07)	0.81
Total frequency of all activities per month	0.99 (0.96, 1.03)	0.94	0.98 (0.95, 1.01)	0.33	0.98 (0.94, 1.02)	0.42
Ratio of aerobic activity over all activity per month	1.06 (0.78, 1.44)	0.68	0.98 (0.79.1.21)	0.87	0.79 (0.58, 1.09)	0.16
Ratio of strength training activity over all activity per month	0.91 (0.65, 1.27)	0.60	1.09 (0.79, 1.21)	0.87	0.79 (0.58, 1.09)	0.16
Weekly frequency of strenuous activity						
<2 times per week	Ref		Ref		Ref	
3-4 times per week	1.06 (0.86, 1.31)	0.56	1.08 (0.93, 1.25)	0.28	0.91 (0.74, 1.12)	0.39
5-6 times per week	1.04 (0.78, 1.40)	0.75	1.15 (0.93, 1.43)	0.18	1.01 (0.73, 1.40)	0.93
7+ times per week	0.94 (0.61, 1.44)	0.79	1.19 (0.88, 1.61)	0.23	1.25 (0.80, 1.96)	0.32
Average duration of strenuous activity sessions						
<15 minutes/session	Ref		Ref		Ref	
15-29 minutes/session	1.02 (0.80, 1.29)	0.84	1.10 (0.93, 1.30)	0.24	0.63 (0.23, 1.69)	0.36
30+ minutes/session	0.88 (0.70, 1.10)	0.28	1.09 (0.93, 1.27)	0.28	1.54 (0.70, 3.39)	0.28
Weekly frequency of moderate activity						
<2 times per week	Ref		Ref		Ref	
3-4 times per week	0.94 (0.74, 1.18)	0.61	1.13 (0.96, 1.33)	0.12	0.93 (0.75, 1.16)	0.55
5-6 times per week	1.11 (0.84, 1.47)	0.43	1.21 (0.99, 1.49)	0.06	1.39 (1.06, 1.82)	0.02
7+ times per week	1.08 (0.75, 1.53)	0.66	1.14 (0.86, 1.50)	0.34	1.20 (0.81, 1.78)	0.35
Average duration of moderate activity sessions						
<15 minutes/session	Ref		Ref		Ref	
15-29 minutes/session	0.91 (0.71, 1.16)	0.47	1.07 (0.90, 1.28)	0.41	0.90 (0.71, 1.14)	0.40
30+ minutes/session	0.91 (0.72, 1.15)	0.46	0.99 (0.83, 1.18)	0.97	1.12 (0.89, 1.41)	0.30

[a] Models are adjusted on: age, race (white/non-white), family history of cancer (yes/no), number of servings of fruit and vegetables eaten per day, number of alcoholic drinks per day, smoking status (ever/never/former), and smoking pack years.

[b] Body mass index (BMI) was calculated using self-reported height and weight data collected from the SQX questionnaire.

[c] Hazard ratios and p-values emboldened represent those rates that maintained significance after applying the Benjamini-Hochberg correction procedure with a false discovery rate of 0.10.

[d] Aerobic activities included: aerobics, cycling, dancing, jogging, swimming, and walking one mile without stopping.

[e] Strength training activities included: gardening, weight lifting, and calisthenics. Gardening categorized as a strength based activity according to the National Institutes of Health: https://www.nhlbi.nih.gov/health/health-topics/topics/phys/types

We found that cancer risk in obese women was mitigated by physical activity, specifically aerobic activity, and that the greater the total frequency of time spent in any physical activity, the greater the overall cancer risk reduction. Aerobic activity's benefits for cancer prevention have been identified in many previous studies examining physical activity benefits in specific cancers, including breast and colorectal cancer. That the protective effects for all-cancer incidence are only seen in obese women may support theories of overlapping biomechanisms involved in both obesity and cancer, including increased leptin production, increased insulin-like growth factor, and imbalances in sex-hormones, all of which are improved through physical activity.

Interestingly, we did not find any significant effect of physical activity on all-cancer incidence in men of any BMI. This may suggest that the interaction between physical activity and obesity does not affect men in the same way it affects women. Our findings are similar to a recent study by Elwood et al. conducted on lifestyle behaviors in men, which found that no lifestyle factors, including physical activity, impacted cancer incidence in men.[18] A study in 2015 by Taghizadeh et al. found that while chronic obesity was associated with increased cancer mortality in women only, both short-term increases in obesity and being overweight was associated with a decreased risk of certain cancers in men, including prostate cancer and lung cancer.[19] The authors postulated that as obesity is strongly associated with cardiovascular mortality in men, it is possible that many at-risk men had already died from cardiovascular disease before they could develop cancer.[19] It is also possible that men who smoke are more likely to remain lean, though at increased cancer risk.[19] More research is needed to identify how adiposity interacts with cancer risk in men, in order to fully understand how the biological mechanisms between obesity and male risk of cancer are associated.

Our study had several limitations. As has been reported previously, our cohort tended to be both older and healthier than the general population, which may limit the generalizability of our findings.[20] Additionally, our data relied on self-reported physical activity, dietary, and lifestyle information, which could be subject to bias.[21] However, as our outcome was cancer incidence, it can be argued that more accurate data would only magnify our findings, as participants are more likely to overestimate their physical activity in self-report. Finally, our participants were followed for 7 years after reporting physical activity information. This may not have been sufficient follow-up time to identify all cancers associated with lifestyle behaviors.

Cancer is an aggregate disease – not a specific condition but, rather, a term used to describe unregulated cell growth across the entire body, caused by different etiologic factors. As such, it may seem counterintuitive to attempt to identify any general factors that contribute to the condition. However, when attempting to disseminate health information to the public, broad recommendations for prevention can be useful in health communication messaging. We recommend concerted efforts by both healthcare providers and public health officials to encourage obese women to increase total and specifically aerobic physical activity to reduce their risk of cancer.

References

1. Ballard-Barbash R, Friedenreich C, Slattery M, Thune I. Obesity and Body Composition. In: *Cancer, Epidemiology and Prevention*. 3rd ed. Oxford University Press; 2006.

2. Friedenreich CM, Nielson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. *Euro J Cancer*. 2010;46(14):2593-2604. doi:10.1016/j.ejca.2010.07.028.

3. Arem H, Moore SC, Park Y, et al. Physical activity and cancer-specific mortality in the NIH-AARP Diet and Health Study cohort. *Int J Cancer*. 2014;135(2):423-431. doi:10.1002/ijc.28659.

4. Li T, Wei S, Shi Y, et al. The dose-response effect of physical activity on cancer mortality: findings from 71 prospective cohort studies. *Br J Sports Med*. 2016;50(6):339.

5. McTiernan A. Mechanisms linking physical activity with cancer. *Nat Rev Cancer*. 2008;8:205-211. doi:10.1038/nrc2325.

6. Renehan AG, Zwhalen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (ICF)-I, IGF binding protein-3, and cancer-risk: systematic review and meta-regression analysis. *Lancet*. 2004; 363(9418):1346-1353.

7. Tili E, Michaille J, Wernicke D, et al. Mutator activity induced by microRNA-155 (mir-155) links inflammation and cancer. *PNAS*. 2011;108(12):4908-4913. doi:10.1073/pnas.1101795108.

8. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol*. 2011; 11:607-615. doi:10.1038/nri3041.

9. Vucenik I, Stains JP. Obesity and cancer risk: evidence, mechanisms, and recommendations. *Ann NY Acad Sci*. 2012;1271:37-43. doi:10.1111/j.1749-6632.2012.06750.x.

10. Michaud DS, Giovannucci E, Willet WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height and the risk of pancreatic cancer. *JAMA*. 2001;286(8):921-929.

11. Pierce JP, Stefanick ML, Flatt SW, et al. Greater survival after breast cancer in physically active women with high vegetable-fruit intake, regardless of obesity. *Am Soc Clin Onc*. 2007;25(17):2345-2351.

12. Qatanani M, Lazar MA. Mechanisms of obesity-associated insulin resistance: many choices on the menu. *Genes & Dev*. 2007;21:1443-1445. doi:10.1101/gad.1550907.

13. Pasquali R. Obesity and androgens: facts and perspectives. *Fertility & Sterility*. 2006;85(5):1319-1340. doi:10.1016/j.fertnstert.2005.10.054.

14. Centers for Disease Control and Prevention (2015). "How much physical activity do older adults need?"

15. Accessed September 13, 2015.

16. Friedenreich CM. Physical activity and breast cancer: review of the epidemiologic evidence and biological mechanisms. *Recent Results Cancer Res*. 2011;188:125-139.

17. Gren L, Broski K, Childs J. Recruitment methods employed in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. *Clin Trials*. 2009;6:52-59. doi:10.1177/1740774508100974.

18. Porok PC, Andriole GL, Bresalier RS. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials*. 2000;21:273S-309S.

19. Elwood P, Galante J, Pickering J, et al. Healthy lifestyles reduce the incidence of chronic diseases and dementia: evidence from the Caerphilly Cohort Study. *PLoS One*. 2013;8(12):e81877. doi:10.1371/journal.pone.0081877.

20. Taghizadeh N, Boezen HM, Schouten JP, Schroder CP, de Vries EGE, Vonk JM. BMI and lifetime changes in BMI and cancer mortality risk. *PLoS One*. 2015;10(4): e0125261. doi:10.1371/journal.pone.0125261.

21. Pinksy PF, Miller A, Kramer T, et al. Evidence of a health volunteer effect in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. *Am J Epidemiol*. 2007;165(8):874-881.

22. Prince SA, Adamo KB, Hamel ME, Hardt J, Gorber SC, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in daults: a systematic review. *Int J Behav Nutr Phys Act*. 2008;5(56). doi:10.1186/1479-5868-5-56.

CHAPTER 3

EXAMINING THE ROLE OF SPECIFIC PHYSICAL ACTIVITY ATTRIBUTES IN BREAST, COLORECTAL, ENDOMETRIAL, LUNG, OVARIAN, AND PROSTATE CANCERS

Abstract

There is growing evidence that physical activity decreases cancer risk. Though the majority of evidence centers around breast and colorectal cancers, evidence for prevention of other types of cancer, such as endometrial, lung, and prostate cancers, is also increasing. Yet, little existing research has clarified which specific attributes of physical activity (e.g., intensity, activity type, frequency) contribute to this risk reduction. Public health recommendations around physical activity and cancer may be more effective if they are more actionable.

Our study assessed several specific attributes of physical activity (type, frequency, intensity, and duration) and their relationship to cancer incidence, using participant data from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Cox proportional hazards models were used to estimate hazard ratios and 95% CIs for associations between the physical activity variables of interest and separate cancer outcomes for breast, colorectal, endometrial, lung, ovarian, and prostate cancers.

After adjustment for multiple test correction, to reduce the likelihood of Type 1 error, none of our findings were statistically significant. Future studies looking to assess

specific attributes of physical activity should ensure that they are powered to detect effect, that physical activity variables are collected in a standardized fashion that allows computation of metrics that relate to guidelines, and that the potential effect modification of body mass is accounted for in study design.

Introduction

There is a growing body of evidence supporting the important role of physical activity in primary, secondary, and tertiary prevention of cancer. The majority of evidence centers on the role of physical activity in improving morbidity and mortality outcomes in individuals diagnosed with cancer.[1] However, evidence for primary prevention of cancer is increasing, particularly for certain cancer types.[2]

The strongest evidence for the role of physical activity in preventing cancer can be found in breast, colorectal, and endometrial cancer research. Weaker evidence exists for the role of physical activity in prevention of prostate, lung, or ovarian cancer.

Breast Cancer

The majority of evidence supports the role of physical activity in breast cancer prevention in postmenopausal women. Estimates of risk reduction due to physical activity are about 10-20%, depending on the study.[3] A recent pooled analysis of 63,786 cases from several large trials, including the Framingham Heart Study, the Nurses Health Study, the NHANES study, and others, found an overall risk reduction from physical activity of 0.88 (95% CI: 0.85-0.91), while a recent pooled analysis of 1.44 million participants, from many of the same trials with the addition of some European data, found a BMI-adjusted hazard ratio of 0.93 (95% CI: 0.90, 0.96) when comparing individuals who completed high levels of physical activity to those who were largely sedentary.[4-5]

Stronger associations for physical activity and risk reduction exist for recreational activity compared to occupational activity for women with normal body mass index (BMI), and women who did not have a family history of cancer.[4,6] Activity after the age of 50 appeared to be a stronger predictor of effect than activity over the life course.[6] Additionally, the effect of physical activity was stronger in women who participated in vigorous intensity physical activity, compared to women who participated in low or moderate physical activity.[4] Current recommendations for prevention are 4-7 hours of vigorous activity per week to prevent breast cancer in postmenopausal women.[6]

More limited evidence supports the role of physical activity in reducing breast cancer incidence in premenopausal women. A prospective study of premenopausal women conducted by Maruti et al. in 2008 found that women with higher total lifetime physical activity had a significantly lower risk of breast cancer compared to inactive women (RR: 0.77, 95% CI: 0.64, 0.93); however, this correlation was not seen in overweight women.[7] Differences in premenopausal breast cancer risk by weight have been found in several studies, with mixed outcomes. Studies by both Maruti[7] and Wu[4] found physical activity reduced the risk of breast cancer in premenopausal women, while McCullough et al.[8] found no significance. A systematic review conducted by Friedenreich et al.[6] found that menopausal status changes the interaction of physical activity and cancer outcomes, but that both pre- and postmenopausal women benefit from increased physical activity.

A main etiologic mechanism affecting breast cancer risk is higher body weight. Increased adipose tissue influences hormonal balances, including estrogen, androgens, sex-hormone binding globulin (SHBG), and insulin resistance.[9] Relatively high levels of physical activity are associated with lower levels of adiposity and weight maintenance, and may therefore result in less androgen conversion to estrogen and bioavailability of estradiol through the increase of SHBG in highly active women.[9] Physical activity also improves insulin sensitivity, potentially by reduction of abdominal fat and increasing glucose transport to muscle and decreasing fatty acid synthesis.[9] The amount or intensity of physical activity necessary to improve these biomarkers remains unclear. A recent 12-month prospective cohort of previously inactive postmenopausal women conducted by Farris et al. found no significant differences between women who exercised at high levels (300 minutes/week) compared to moderate levels (150 minutes/week) in terms of estradiol, SHBG, and estrone, suggesting the exact physical activity prescription, including type and intensity, needed to affect these factors is still unclear.[10] Nonetheless, the evidence on the effect of physical activity for reducing susceptibility to breast cancer remains one of the most compelling cancer-related benefits of physical activity to date.

Colorectal Cancer

Strong evidence also exists supporting the role of physical activity in colorectal cancer prevention. A meta-analysis of existing evidence conducted by Wolin et al.[11] found an inverse relationship between physical activity and colorectal cancer, with an overall relative risk of 0.76 (95% CI: 0.72, 0.81). The pooled analyses of 1.44 million participants conducted by Moore et al.[5] similarly found reduced risk of cancer in highly active individuals, compared to inactive individuals (HR: 0.87, 95% CI: 0.77, 0.98). The majority of existing evidence specifically indicates that increased recreational and leisure time physical activity significantly decreases the risk of developing colorectal cancer.[5,11]

Like breast cancer, there are subsets of individuals who are more impacted by physical activity than others. For example, the majority of research pertains to individuals who are diagnosed with cancer of the colon, not the rectum, though some studies did not distinguish between the two. Most evidence that differentiated the two cancer sites collected to date has not found a significant association between physical activity and rectal cancer.[2,11,12] However, risk reductions associated with physical activity do not appear to be significantly different between proximal and distal colon cancers.[13] There do not appear to be sex differences in risk; a systematic review conducted by Brown et al.[2] found no differences in the association between physical activity and colorectal cancer risk in men compared to women.

There are several biological mechanisms that have been posited as etiologic factors in the relationship between physical activity and colorectal cancer, including the role of physical activity in decreasing inflammation, improving digestion, reducing intestinal transit time, improving immune function, and in moderating the insulin-like-growth factor axis.[2]

Endometrial Cancer

The body of evidence supporting the role of physical activity in reducing the risk of endometrial cancer is growing. Several meta-analyses of the literature have found compelling evidence that high levels of leisure and recreational activity reduce the risk of endometrial cancer by up to 30% in postmenopausal women.[6,14,15] As with colorectal and breast cancers, the role of body mass also factors in to considerations of risk reduction for endometrial cancer, with some studies suggesting that overweight or obese women who are physically active may see more of a risk reduction than women who are lean.[16,17]

Etiologic factors at play in the interaction between physical activity and endometrial cancer risk are thought to be similar to those in breast cancer, with physical activity playing a role in moderating hormone balance, including androgens, estrogens, and SHBG, the dysregulation of which are believed to be causal pathways in endometrial cancer. Insulin-like growth factor is also a known risk agent for endometrial cancer and is also regulated by physical activity.[18] Ultimately, much of the benefit of physical activity in endometrial cancer risk may be in counteracting the negative biological effects of high body mass.[17,19]

Ovarian Cancer

Whether physical activity plays a role in the prevention of ovarian cancer is not clear. Studies had mixed results, with some, such as those from Lee et al.,[20] supporting risk reduction (OR: 0.49, 95% CI: 0.35, 0.68) and others, such as Moorman[21] (HR: 0.69, 95% CI: 0.47, 1.00) and Chionh[22] (HR: 2.21, 95% CI: 1.16, 4.24), suggesting null or increased risk. A meta-analysis conducted by Cannioto[23] found that the majority of the existing evidence supports physical activity resulting in some risk reduction; however, the evidence is far from conclusive and more studies are needed to more firmly establish this connection. Cannioto et al.[23] speculate that the lack of significant findings may be due to the large variety in histology between ovarian cancers; some types of ovarian cancers may be more influenced by physical activity than others.

Proposed biological mechanisms for physical activity influence on ovarian cancer risk include moderating the role of sex hormones and its role in reducing chronic inflammation.[23]

Prostate Cancer

The evidence surrounding the role of physical activity in prevention of prostate cancer is also mixed. A systematic review by Hackshaw-McGeah et al.[24] found no high-quality studies with significant findings associating physical activity with reduced risk for prostate cancer. Other earlier systematic reviews and meta-analyses, such as Liu et al.,[25] have found some associations between physical activity and prostate cancer (pooled RR: 0.90, 95% CI: 0.84, 0.95). Some studies have found that risk reduction from physical activity may differ by race, with African American men more affected by physical activity than white men[26]; other studies have contradicted these findings, suggesting no significant differences in risk reduction from physical activity between races.[27] Studies on physical activity and prostate cancer appear to have more statistically significant findings in American and European populations, compared to Asian and Pacific Islander populations.[25] Similarly, some evidence supports the role of early physical activity in reducing the risk of prostate cancer later in life,[26] while other studies have not found that early activity plays a significant role in subsequent risk reduction.[25]

The role of insulin-like growth factor (IGF) is thought to be a main etiologic mechanism involved in the relationship between physical activity and cancer. Physical activity increases production of IGF, the binding of which affects cell proliferation and migration, thus leading to decreased risk of cancer.[28]

Lung Cancer

Evidence of an inverse relationship between physical activity and risk for lung cancer has been increasing. A meta-analysis by Zhong et al.[29] found that individuals who had participated in any amount of physical activity had a risk ratio of 0.79 (95% CI: 0.73, 0.86) for developing lung cancer. Those who had participated in a higher level of physical activity had a greater risk reduction.[29]

The relationship between physical activity and lung cancer seems to be impacted by smoking status. A pooled analysis by Buffart et al.[30] found that physically active smokers had a reduced risk of lung cancer compared to nonactive smokers. The difference did not appear to be impacted by smoking intensity, but was greater for women than for men.[30] The meta-analysis conducted by Zhong et al.[29] did not find any impact of physical activity on nonsmokers who later developed lung cancer. As the etiology of nonsmokers who develop lung cancer is different from that of individuals who smoke, it is likely that physical activity affects risk differently in these subgroups. One study by Lam et al.[31] showed that nonsmoking individuals who were overweight at the age of 18 had a 46% increased risk of lung cancer, compared to individuals who were normal weight.

For smokers, physical activity is theorized to improve pulmonary function and enhance the expulsion of carcinogenic material from the lungs, thus decreasing the risk for lung cancer.[29,32] In nonsmokers, the relationship is less clear, but appears to be influenced to a certain degree by sedentary behaviors and obesity.

While the evidence surrounding the role of physical activity is increasing for different types of cancers, questions still remain about how physical activity type, intensity, frequency, and duration influence cancer risk across the cancer types. The purpose of the current study was to assess these physical activity variables and their relationship to differing cancer outcomes in individuals participating in a large, cancer screening study.

Methods

Participants for this study were men and women who participated in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), a randomized controlled trial conducted from 1993 until 2013 designed to determine the effect of screening on mortality from these four cancers.[33] Enrollment for the trial occurred from 1993 until 2001. Participants were followed for at least 13 years after enrollment. Details regarding recruitment and enrollment can be found elsewhere.[34] Upon enrollment, participants provided demographic, personal, and family disease history data. They also completed a dietary history questionnaire and answered questions regarding current physical activity. In 2006, a supplemental questionnaire (SQX) was collected, which included more in-depth questions about physical activity and exercise, including the types of physical activity engaged in monthly, weekly frequency of activity, and subjective assessment of activity intensity (strenuous, moderate, and light). Annual data collection for the PLCO trial was completed in 2009.

Of the total PLCO participants (n =154,898), those included in this study were individuals who: 1) had complete baseline and dietary history information (n=149,978), 2) had completed the physical activity questions on the SQX questionnaire (n=100,704), 3) did not have a diagnosis of cancer at the time of SQX data collection (n=85,430), and 4) had follow-up data up through year 13 of study enrollment (n=78,687) (see Figure 3.1). Of these, 36,969 (46%) were men and 41,718 (54%) were women. Table 3.1 provides a demographic overview of participants. The current study was approved by the University of Utah Institutional Review Board.

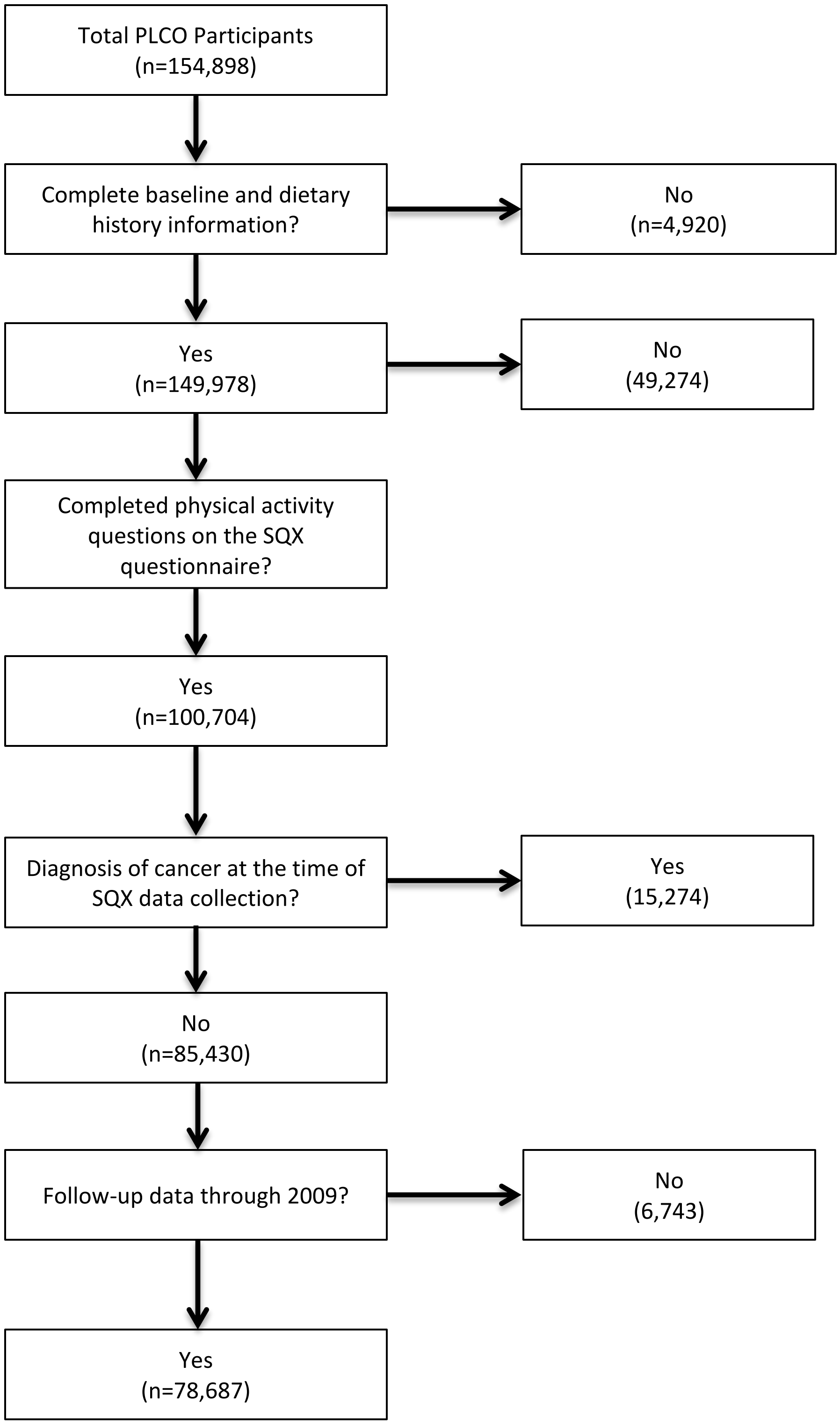

Figure 3.1. Consort Diagram of Participant Selection

Table 3.1. Demographic Table of Participants from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Study Population

Variable	No Cancer (n=74,713)	Breast (n=631)	Colorectal (n=209)	Endometrial (n=96)	Ovarian (n=59)	Prostate (n=1,050)	Lung (n=394)
Sex							
Female	53.6%	100%	58.4%	100%	100%	N/A	56.6%
Male	46.4%	N/A[a]	41.6%	N/A	N/A	100%	43.4%
Average age at randomization	61.8	61.7	63.4	60.7	62.1	61.3	62.5
Race							
American Indian	0.1%	0.0%	0.5%	0.0%	0.0%	0.1%	0.0%
Asian	3.4%	2.1%	1.9%	2.1%	3.4%	3.7%	2.8%
Black	2.8%	3.2%	3.4%	4.3%	1.7%	3.1%	4.1%
Hispanic	0.9%	0.8%	0.0%	1.1%	0.0%	1.6%	0.8%
Pacific Islander	0.4%	0.3%	0.0%	0.0%	0.0%	0.3%	0.5%
White	89.1%	92.4%	87.6%	91.5%	94.9%	90.1%	89.5%
Unknown	3.3%	1.3%	6.7%	1.1%	0.0%	1.2%	2.3%
Family history of cancer							
Yes	55.7%	64.4%	59.3%	55.2%	59.3%	53.8%	59.7%
No	44.3%	35.6%	40.7%	44.8%	40.7%	46.2%	40.3%
Body mass index							
<25 – Normal or underweight	33.9%	32.2%	25.7%	30.2%	40.7%	74.8%	39.6%
≥25 – Overweight or obese	66.1%	67.8%	74.2%	69.8%	59.3%	25.2%	60.4%
Smoking status							
Never	46.9%	56.2%	44.4%	63.4%	56.9%	39.7%	10.5%
Former smoker	46.9%	37.9%	50.5%	34.4%	34.5%	54.1%	57.3%
Current smoker	6.2%	5.8%	5.1%	2.2%	8.6%	6.2%	32.2%
Average smoking pack years	17.9	14.2	22.3	8.8	11.2	21.2	53.7
Average number of alcoholic drinks per day	0.78	0.46	0.78	0.45	0.67	1.19	1.09
Average fruit consumed per day	2.74	2.69	2.86	2.61	2.60	2.47	2.34
Average vegetables consumed per day	3.93	3.71	4.07	4.00	3.90	3.86	3.71

[a] Four eligible male participants were diagnosed with breast cancer; however, for the purposes of this study, these individuals were not assessed in the overall analysis, due to the differing risk factors that affect male breast cancer incidence.

Physical Activity Variables

Using the physical activity variables obtained from the SQX questionnaire, we created two composite variables of activity frequency. We first divided reported variables into aerobic and strength type categories. We then created composite variables for total aerobic and total strength activities, by adding all self-reported weekly frequency of specific activities (e.g., 2 times dancing, 2 times jogging, 2 times swimming would equal 6 times of aerobic activity in one week). We then created a variable for total frequency of all reported activity (strength and aerobic combined).

We were also interested in examining how proportion of time spent in a specific type of activity influenced cancer outcomes. For example, if an individual is highly active, but only does strength training activities (compared to aerobic activities), does it affect their risk differently than an individual who divides time more evenly between activity types? To assess this, we created two ratio variables, which identified the proportion of total activity frequency spent in either type of activity.

We were also interested in exploring variables of intensity and duration. The SQX questionnaire asked questions around weekly frequency of strenuous and moderate activity, as well as questions about the average duration of each strenuous/moderate activity session. Unfortunately, due to the categories created within the SQX for these variables, we were unable to combine them for a more standard measure of total weekly time spent in strenuous or moderate activity. Nonetheless, we explored the intensity and duration variables separately in our analyses.

Statistical Analyses

We conducted separate analyses for specific cancers, including breast, ovarian, endometrial, and prostate cancers. We also conducted sex-specific analyses for lung and colorectal cancers.

We explored all variables listed in Table 3.1 as potential confounders or covariates in the model and retained all variables that were statistically significant ($p<0.05$) in univariate analyses or were supported by existing literature as associated with cancer incidence. The linearity of the various PA variables was assessed using likelihood ratio tests. Additionally, we conducted sensitivity analyses to assess the effect of outlier extremes on physical activity variables.

Physical Activity Variables

Using the physical activity variables obtained from the SQX questionnaire, we created two composite variables of activity frequency. We first divided reported variables into aerobic and strength type categories. We then created composite variables for total aerobic and total strength activities, by adding all self-reported weekly frequency of specific activities (e.g., 2 times dancing, 2 times jogging, 2 times swimming would equal 6 times of aerobic activity in one week). We then created a variable for total frequency of all reported activity (strength and aerobic combined).

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Statistical Analyses

We conducted separate analyses for specific cancers, including breast, ovarian, endometrial, and prostate cancers. We also conducted sex-specific analyses for lung and colorectal cancers.

We explored all variables listed in Table 3.1 as potential confounders or covariates in the model and retained all variables that were statistically significant ($p<0.05$) in univariate analyses or were supported by existing literature as associated with cancer incidence. The linearity of the various PA variables was assessed using likelihood ratio tests. Additionally, we conducted sensitivity analyses to assess the effect of outlier extremes on physical activity variables.

Hazard ratios and 95% confidence intervals (CIs) were estimated using Cox proportional hazard regression models to assess the association between physical activity variables and cancer incidence. We analyzed specific physical activity variables with relation to separate prostate, lung, colon, ovarian, breast, and endometrial cancer outcomes. Follow-up time was defined as all time after completion of the SQX questionnaire (in 2006) until cancer diagnosis or through 2013, whichever occurred first. Following regression analyses, we applied the Benjamini-Hochberg procedure for multiple test correction with a false discovery rate of 0.10 to all findings (McDonald, 2014 pp. 254-260).[35] All analyses were conducted in Stata 12.0. This study was approved by the Institutional Review Board of the University of Utah.

Results

Tables 3.2–3.6 provide outcomes of all physical activity variables and specific cancer incidence. After adjusting for multiple test correction, no variables maintained significance in the final analyses. The frequency of moderate and strenuous activity appeared to increase the risk of ovarian (4-5x/week, HR: 2.27; 95% CI: 1.00, 5.17), prostate ([4-5x/week, HR: 1.31; 95% CI: 1.06, 1.61] and [6-7x/week, HR: 1.40; 95% CI: 1.07, 1.82]), and colorectal cancer in women (6-7x/week, HR: 3.12; 95% CI: 1.19, 8.15). It also appeared to decrease the risk of lung cancer in women (4-5x/week, HR: 0.38; 95% CI: 0.15, 0.96). As none of these increases or decreases demonstrated any sort of dose-response relationship, it is possible that these findings were spurious.

Discussion

Thus far, the available evidence in the literature supporting the role of physical activity in the prevention of cancer is most convincing for breast and colorectal cancer, yet, after adjusting for multiple test correction, our results did not find significance for any cancer outcomes: breast, colorectal, or otherwise. Our previous study with this cohort examined the association of physical activity variables on all-cancer incidence and found a significantly decreased risk for all-cancer incidence in obese women who participated in aerobic physical activity.[36] The current findings for breast, colorectal, and lung cancer

Table 3.2. Associations between Self-Reported Physical Activity Variables and Breast Cancer Incidence in Female Participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Study Population[a]

Type of physical activity	Outcomes	
	HR (95% CI)	p
Total monthly aerobic activity[b] frequency	0.99 (0.92, 1.06)	0.84
Total monthly strength training[c] frequency	1.04 (0.98, 1.11)	0.16
Total frequency of all activities per week	1.01 (0.97, 1.05)	0.43
Ratio of aerobic activity over all activity per week	0.79 (0.59, 1.05)	0.11
Ratio of strength training activity over all activity per week	1.28 (0.95, 1.73)	0.09
Total frequency of strenuous activity per week		
< 2 sessions per week	Ref	
2-3 sessions per week	1.01 (0.81, 1.24)	0.91
4-5 sessions per week	1.23 (0.90, 1.67)	0.18
6-7 sessions per week	1.16 (0.69, 1.93)	0.56
Average duration of strenuous activity session		
<15 minutes	Ref	
15-29 minutes	1.12 (0.89, 1.42)	0.30
30+ minutes	1.08 (0.86, 1.35)	0.45
Total frequency of moderate activity per week		
<2 sessions per week	Ref	
2-3 sessions per week	1.01 (0.81, 1.25)	0.92
4-5 sessions per week	1.05 (0.79, 1.40)	0.71
6-7 sessions per week	1.02 (0.67, 1.55)	0.91
Average duration of moderate activity session		
<15 minutes	Ref	
15-29 minutes	0.86 (0.67, 1.10)	0.23
30+ minutes	1.15 (0.91, 1.45)	0.21

[a] Models are adjusted on: age, race, age at first menstruation, age at menarche, number of pregnancies, birth control use (ever/never), Body Mass Index (BMI), hormone replacement therapy status (current/ever/never), family history of cancer, number of servings of fruit and vegetables eaten per day, number of alcoholic drinks per day, hormone replacement therapy status (ever/never/former), smoking status (ever/never/former), and smoking pack years.

[b] Aerobic activities included: aerobics, cycling, jogging, swimming, dancing, and walking one mile without stopping.

[c] Strength training activities included: weight lifting, gardening, and calisthenics. Gardening is categorized as a strength-based activity according to the National Institutes of Health: https://www.nhlbi.nih.gov/health/health-topics/topics/phys/types

Table 3.3. Associations between Self-Reported Physical Activity Variables and Endometrial Cancer Incidence in Female Participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Study Population[a]

	Outcomes	
Type of physical activity	HR (95% CI)	p
Total monthly aerobic activity[b] frequency	0.91 (0.75, 1.10)	0.34
Total monthly strength training[c] frequency	0.88 (0.73, 1.06)	0.18
Total frequency of all activities per week	0.91 (0.80, 1.03)	0.14
Ratio of aerobic activity over all activity per week	1.05 (0.48, 2.29)	0.88
Ratio of strength training activity over all activity per week	0.89 (0.40, 1.99)	0.78
Total frequency of strenuous activity per week		
< 2 sessions per week	Ref	
2-3 sessions per week	1.22 (0.71, 2.09)	0.45
4-5 sessions per week	0.90 (0.35, 2.33)	0.83
6-7 sessions per week	1.62 (0.49, 5.33)	0.42
Average duration of strenuous activity session		
<15 minutes	Ref	
15-29 minutes	1.21 (0.68, 2.18)	0.50
30+ minutes	0.88 (0.47 1.64)	0.69
Total frequency of moderate activity per week		
<2 sessions per week	Ref	
2-3 sessions per week	0.81 (0.46, 1.42)	0.46
4-5 sessions per week	0.95 (0.44, 2.01)	0.89
6-7 sessions per week	1.47 (0.57, 3.55)	0.44
Average duration of moderate activity session		
<15 minutes	Ref	
15-29 minutes	0.94 (0.50, 1.76)	0.86
30+ minutes	1.09 (0.59, 2.02)	0.76

[a] Models are adjusted on: age, race, age at first menstruation, age at menarche, number of pregnancies, birth control use (ever/never), Body Mass Index (BMI), family history of cancer, number of servings of fruit and vegetables eaten per day, number of alcoholic drinks per day, hormone replacement therapy status (ever/never/former), smoking status (ever/never/former), and smoking pack years.

[b] Aerobic activities included: aerobics, cycling, jogging, swimming, dancing, and walking one mile without stopping.

[c] Strength training activities included: weight lifting, gardening, and calisthenics. Gardening is categorized as a strength-based activity according to the National Institutes of Health: https://www.nhlbi.nih.gov/health/health-topics/topics/phys/types

Table 3.4. Associations between Self-Reported Physical Activity Variables and Ovarian Cancer Incidence in Female Participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Study Population[a]

Type of physical activity	Outcomes HR (95% CI)	p
Total monthly aerobic activity[b] frequency	0.95 (0.77, 1.17)	0.64
Total monthly strength training[c] frequency	1.01 (0.96, 1.09)	0.34
Total frequency of all activities per week	0.99 (0.87, 1.12)	0.87
Ratio of aerobic activity over all activity per week	0.93 (0.39, 2.22)	0.88
Ratio of strength training activity over all activity per week	1.15 (0.46, 2.87)	0.76
Total frequency of strenuous activity per week		
< 2 sessions per week	Ref	
2-3 sessions per week	1.22 (0.65, 2.27)	0.52
4-5 sessions per week	1.20 (0.45, 3.17)	0.71
6-7 sessions per week	1.43 (0.33, 6.14)	0.62
Average duration of strenuous activity session		
<15 minutes	Ref	
15-29 minutes	1.79 (0.95, 3.37)	0.07
30+ minutes	0.75 (0.34, 1.64)	0.47
Total frequency of moderate activity per week		
<2 sessions per week	Ref	
2-3 sessions per week	1.43 (0.70, 2.93)	0.31
4-5 sessions per week	2.27 (1.00, 5.17)	0.05[d]
6-7 sessions per week	0.93 (0.20, 4.23)	0.92
Average duration of strenuous activity session		
<15 minutes	Ref	
15-29 minutes	1.50 (0.73, 3.07)	0.26
30+ minutes	0.96 (0.44, 2.09)	0.92

[a] Models are adjusted on: age, race, age at first menstruation, age at menarche, number of pregnancies, birth control use (ever/never), Body Mass Index (BMI), family history of cancer, number of servings of fruit and vegetables eaten per day, number of alcoholic drinks per day, hormone replacement therapy status (ever/never/former), smoking status (ever/never/former), and smoking pack years.

[b] Aerobic activities included: aerobics, cycling, jogging, swimming, dancing, and walking one mile without stopping.

[c] Strength training activities included: weight lifting, gardening, and calisthenics. Gardening is categorized as a strength-based activity according to the National Institutes of Health: https://www.nhlbi.nih.gov/health/health-topics/topics/phys/types

[d] After applying the Benjamini-Hochberg procedure for multiple test correction, this finding is no longer significant.

Table 3.5. Associations between Self-Reported Physical Activity Variables and Prostate Cancer Incidence in Male Participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Study Population[a]

Type of physical activity	Outcomes HR (95% CI)	p
Total monthly aerobic activity[b] frequency	1.01 (0.96, 1.06)	0.53
Total monthly strength training[c] frequency	1.00 (0.96, 1.04)	0.81
Total frequency of all activities per week	1.00 (0.97, 1.03)	0.60
Ratio of aerobic activity over all activity per week	0.98 (0.79, 1.22)	0.90
Ratio of strength training activity over all activity per week	1.13 (0.89, 1.44)	0.28
Total frequency of strenuous activity per week		
< 2 sessions per week	Ref	
2-3 sessions per week	1.15 (0.99, 1.34)	0.06
4-5 sessions per week	1.22 (0.98, 1.51)	0.07
6-7 sessions per week	1.20 (0.88, 1.64)	0.23
Average duration of strenuous activity session		
<15 minutes	Ref	
15-29 minutes	1.08 (0.90, 1.28)	0.37
30+ minutes	1.11 (0.95, 1.31)	0.17
Total frequency of moderate activity per week		
<2 sessions per week	Ref	
2-3 sessions per week	1.15 (0.97, 1.36)	0.08
4-5 sessions per week	1.31 (1.06, 1.61)	0.01[d]
6-7 sessions per week	1.40 (1.07, 1.82)	0.01[d]
Average duration of strenuous activity session		
<15 minutes	Ref	
15-29 minutes	1.05 (0.87, 1.26)	0.56
30+ minutes	1.13 (0.95, 1.35)	0.15

[a] Models are adjusted on: age, race, Body Mass Index (BMI), family history of cancer, number of servings of fruit and vegetables eaten per day, number of alcoholic drinks per day, smoking status (ever/never/former), and smoking pack years.

[b] Aerobic activities included: aerobics, cycling, jogging, swimming, dancing, and walking one mile without stopping.

[c] Strength training activities included: weight lifting, gardening, and calisthenics. Gardening is categorized as a strength-based activity according to the National Institutes of Health: https://www.nhlbi.nih.gov/health/health-topics/topics/phys/types

[d] After applying the Benjamini-Hochberg procedure for multiple test correction, this finding is no longer significant.

Table 3.6. Associations between Self-Reported Physical Activity Variables and Lung Cancer Incidence in Participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Study Population, Stratified by Sex[a]

	Female lung cancer		Male lung cancer	
Type of physical activity	HR (95% CI)	p	HR (95% CI)	p
Total monthly aerobic activity[b] frequency	0.93 (0.81, 1.06)	0.32	0.96 (0.84, 1.09)	0.54
Total monthly strength training[c] frequency	1.03 (0.91, 1.15)	0.60	0.95 (0.85, 1.06)	0.42
Total frequency of all activities per week	0.98 (0.91, 1.06)	0.78	0.96 (0.90, 1.04)	0.38
Ratio of aerobic activity over all activity per week	0.77 (0.44, 1.34)	0.35	0.94 (0.53, 1.65)	0.83
Ratio of strength training activity over all activity per week	1.08 (0.61, 1.91)	0.78	1.03 (0.55, 1.90)	0.92
Total frequency of strenuous activity per week				
< 2 sessions per week	Ref		Ref	
2-3 sessions per week	0.66 (0.44, 1.00)	0.05[d]	0.90 (0.62, 1.29)	0.57
4-5 sessions per week	0.38 (0.15, 0.96)	0.04[d]	1.05 (0.61, 1.82)	0.84
6-7 sessions per week	1.28 (0.55, 2.96)	0.55	1.43 (0.73, 2.78)	0.29
Average duration of strenuous activity session				
<15 minutes	Ref		Ref	
15-29 minutes	0.75 (0.47, 1.20)	0.24	1.11 (0.75, 1.65)	0.58
30+ minutes	0.83 (0.54, 1.28)	0.42	0.95 (0.64, 1.41)	0.82
Total frequency of moderate activity per week				
<2 sessions per week	Ref		Ref	
2-3 sessions per week	1.05 (0.71, 1.54)	0.78	1.00 (0.68, 1.45)	0.99
4-5 sessions per week	0.64 (0.33, 1.24)	0.19	1.46 (0.90, 2.34)	0.11
6-7 sessions per week	1.26 (0.63, 2.52)	0.50	1.07 (0.54, 2.12)	0.84
Average duration of moderate activity session				
<15 minutes	Ref		Ref	
15-29 minutes	1.14 (0.75, 1.73)	0.53	0.83 (0.56, 1.24)	0.38
30+ minutes	0.97 (0.62, 1.50)	0.89	0.78 (0.52, 1.16)	0.22

[a] Models are adjusted on: sex, age, race, family history of cancer, Body Mass Index, comorbidity score (using PLCO's modified version of the Charleson index for comorbidities), number of servings of fruit and vegetables eaten per day, number of alcoholic drinks per day, smoking status (ever/never/former), and smoking pack years. Female model is also adjusted on age at first menstruation, age at menarche, number of pregnancies, and birth control use (ever/never).

[b] Aerobic activities included: aerobics, cycling, jogging, swimming, dancing, and walking one mile without stopping.

[c] Strength training activities included: weight lifting, gardening, and calisthenics. Gardening is categorized as a strength-based activity according to the National Institutes of Health: https://www.nhlbi.nih.gov/health/health-topics/topics/phys/types

[d] After applying the Benjamini-Hochberg procedure for multiple test correction, this finding is no longer significant.

(cancers with the highest incidence rates for women in the trial) are relatively aligned with our previous findings, though the current results are nonsignificant, suggesting that the higher statistical power of the previous study may have improved our ability to detect an effect.

Our findings of an increased risk for prostate cancer, though not meeting significance after multiple test correction, do have some support in the literature. The recent pooled analysis by Moore et al.[5] also found an increased risk of prostate cancer in highly active males compared to inactive males (HR: 1.05, 95% CI: 1.03, 1.08). Moore hypothesized that this increased risk may be due to the propensity of highly active men to undergo more frequent prostate screening than inactive men, thus identifying more cancers. A recent study by Wang et al.[37] found that individuals who engaged in 17.5 or more MET hours per week decreased the risk of prostate cancer mortality by 30% (HR: 0.70, 95% CI: 0.54-0.92), suggesting that physical activity does provide some etiological benefit to cancer outcomes, which does provide some support to Moore's hypothesis that differential uptake of screening may be influencing risk findings. We had insufficient power to examine cancer mortality as an endpoint.

Frequency of moderate activity was identified with an increased risk for several cancers. Our previous research[36] also identified a nonsignificant increased risk of cancer associated with moderate activity. After adjusting for multiple test correction, none of these variables maintained significance in either analysis and it is unlikely that such results are due to actual correlation and are more likely spurious findings within our data, as they do not demonstrate a dose-response effect that one might expect if an association was involved. These types of findings underscore the importance of collecting strong physical activity data that allow for calculation of best-practice measures of physical activity, such as biological data and MET information for future research.

One reason for our null findings may be the age of our cohort. The average age of participants at enrollment in the trial was 61 years (SE: 0.0183), putting many of our participants closer to age 70 when they completed the SQX. So far, the role of physical activity in preventing cancer over the life course is not completely understood. While some studies have found significant relationships between physical activity and cancer diagnosis in older adults,[16] many studies on physical activity have found that its preventive relationship with cancer is most potent when physical activity occurs at younger ages, specifically in early adulthood.[7,8,38] For sex-specific cancers, such as breast, ovarian, and endometrial cancer, previous research has demonstrated that the effect of physical activity and its role in later cancer prevention is largely dependent on activity levels during the reproductive years.[7,38] In their recommendations for breast cancer prevention, Colditz et al.[3] note that the expected benefit of physical activity is a 10-30 year timeframe, suggesting that to benefit from physical activity later in life, one should most likely engage in physical activity at early ages. While this does not suggest that activity throughout the life course is meaningless, it suggests that accounting for physical activity levels of participants only in their later years may not be an adequate measure of how physical activity variables interact with cancer risk.

Our study did ask participants to report whether their current activity levels were higher, lower, or similar to their activity levels 10 years ago, but initial analysis did not show any differences in cancer incidence between these groups and such categorizations were not pursued in the final model. Again, this may be due to the fact that even the tenyear span comparison within our data was an insufficient proxy for lifetime physical activity, particularly the role it may have played in early life. There is a need for further research to more clearly delineate how physical activity over the life course influences cancer outcomes, particularly if it can assess the role of natural attrition in activity intensity and ability throughout the aging process.

Of interest to this study, and to other studies of its kind, is the role of BMI as an effect modifier. High body mass index has been associated with increased risk for cancer, regardless of physical activity levels.[39] Indeed, our analyses showed that BMI was associated with increased cancer risk for breast, endometrial, and female colon cancer, apart from the physical activity variables being tested (results not shown here). The role of BMI within physical activity is complex, and multidirectional. Individuals with a high BMI who are physically active often demonstrate improved biomarkers (blood pressure, insulin sensitivity, etc.) compared to high BMI individuals who are not active, even if there is not a change in total weight.[40] Yet, since BMI is not simply a marker of inactivity and unhealthy lifestyle, but also has environmental and genetic components that are at play, understanding how it factors into physical activity and cancer risk is as yet unclear. Future studies that are able to assess this relationship in more depth are necessary, to improve risk assessments and recommendations to higher-risk individuals.

One specific method of assessment should be identifying the role of changing body mass over time. Weight loss and weight gain have been shown to change risk calculations,[41,42] but the yo-yo effect of dramatic weight loss and weight gain on potential cancer risk has not been well studied.[43] Since physical activity and other lifestyle changes may result in these increases and decreases, an accounting of such changes is important.

Future studies assessing the association of physical activity with cancer incidence should examine the role of weight loss/gain, specifically during early adulthood and reproductive years, to identify how physical activity and BMI interact in this important life phase.

Findings from the current study provide important insights into how future studies on physical activity and cancer prevention can be improved. Ultimately, studies on older populations should attempt to account for physical activity and BMI throughout the life course as well as currently, in order to better identify how changes over time may impact risk. While evidence of the association between physical activity and cancer continues to grow, there is still a paucity of studies that have been able to identify specific attributes of physical activity that are most effective at reducing risk. This is likely due to the difficulty in obtaining sufficient sample size necessary to stratify data in finer detail and the difficulty of creating a model that appropriately reflects how specific biological mechanisms may change over time, and thus affect risk. For example, older adults do not have the same IGF response associated with physical activity that younger adults do[44]; thus, changes in frequency or intensity of physical activity over the life course may differentially impact cancer incidence, depending on what was occurring when. Nonetheless, such information is important in order to better understand the mechanisms at work within this relationship.

Our study had several limitations. Due to the nature of the variables collected, we were not able to calculate MET (metabolic equivalent) scores for participants' reported activity. As MET scores are widely used in physical activity studies,[45] our inability to calculate them inhibits the generalizability of our study. In addition, the physical activity data we collected was based on data collected at a single time point, rather than data collected throughout the course of the study. As physical activity can change dramatically over time, our study was not able to capture, nor account for, such changes. This may have also been a factor in our lack of significant findings.

Conclusions

Ultimately, our findings suggest that further research is needed to identify which aspects of physical activity specifically affect cancer risk. Future research should ensure that physical activity variables are measured consistently (using gold standard assessments for both self-report and biological measurement). Studies should further investigate the health-conscious screening hypothesis generated by Moore et al.,[5] to better understand the link between increased physical activity and prostate cancer. Additionally, future research that can better tease out the interactions between physical activity, obesity, and cancer will be better poised to provide actionable public health recommendations for cancer prevention.

References

1. Sanchis-Gomar F, Lucia A, Yvert T, et al. Physical inactivity and low fitness deserve more attention to alter cancer risk and prognosis. *Cancer Prev Res* (Phila). 2015;8(2):105-110. doi:10.1158/1940-6207.CAPR-14-0320.

2. Brown JC, Winters-Stone K, Lee A, Schmitz. Cancer, physical activity, and exercise. *Compr Physiol*. 2012;2(4):2775-2809. doi:10.1002/cphys.c120005.

3. Colditz GA, Bohlke K. Priorities for the primary prevention of breast cancer. *CA Cancer J Clin*. 2014;64:186-194. doi:10.3322/caac.21225.

4. Wu Y, Zhang D, Kang S. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. *Breast Cancer Res Treat*. 2013;137:869-882. doi:10.1007/s10549-012-2396-7.

5. Moore SC, Lee I, Weiderpass E, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA Intern Med*. 2016;176(6):816-8125. doi:10.1001/jamainternmed.2016.1548.

6. Friedenreich CM. Physical activity and breast cancer: review of the epidemiologic evidence and biologic mechanisms. *Clin Cancer Prev*. 2010;188):125-139. doi:10.1007/978-3-642-10858_11.

7. Maruti SS, Willett WC, Feskanich D, Rosner B, Colditz GA. A prospective study of age-specific physical activity and premenopausal breast cancer. *J Natl Cancer Inst*. 2008;100:728-737. doi:10.1093/jnci/djn135.

8. McCullough LE, Eng SM, Bradshaw PT, et al. Fat or fit: the joint effects of physical activity, weight gain, and body size on breast cancer risk. *Cancer*. 2012;118:4860-4868. doi:10.1002/cncr.27433.

9. Neilson HK, Friedenreich CM, Brockton NT, Millikan RC. Physical activity and postmenopausal breast cancer: proposed biologic mechanisms and areas for future research. *Cancer Epidemiol Biomarkers Prev*. 2009;18(1):11-27. doi:10.1158/1055-9965.

10. Farris MS, Mosli MH, McFadden AA, Friedenreich CM, Brenner DR. The association between leisure time, physical activity and pancreatic cancer risk in adults: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2015;24(10):1462-1473. doi:10.1158/1055-9965.

11. Wolin KY, Yan Y, Colditz GA, Lee I. Physical activity and colon cancer prevention: a meta-analysis. *Br J Cancer*. 2009;100:611-616. doi:10.1038/sj.bjc.6604917.

12. Spence RR, Heesch KC, Brown WJ. A systematic review of the association between physical activity and colorectal cancer risk. *Scand J Med Sci Sports*. 2009;19:764-781. doi:10.1111/j.1600-0838.2009.00992.x.

13. Boyle T, Keegel T, Bull F, Heyworth J, Fritschi L. Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2012;104(20):1548-1561. doi:10.1093/jnci/djs354.

14. Keum N, Ju W, Lee DH, et al. Leisure-time physical activity and endometrial cancer risk: dose-response meta-analysis of epidemiological studies. *Int J Cancer*. 2014;135:682-694. doi:10.1002/ijc.28687.

15. Moore SC, Gierach GL, Schatzkin A, Matthews CE. Physical activity, sedentary behaviours, and the prevention of endometrial cancer. *Br J Cancer*. 2010;103:933-938. doi:10.1038/sj.bjc.6605902.

16. Dieli-Conwright CM, Ma H, Lacey Jr JV, et al. Long-term and baseline recreational physical activity and risk of endometrial cancer: the California Teachers Study. *Br J Cancer*. 2013;109:761-768. doi:10.1038/bjc.2013.61.

17. Patel AV, Feigelson HS, Talbot JT, et al. The role of body weight in the relationship between physical activity and endometrial cancer: results from a large cohort of US women. *Int J Cancer*. 2008;123:1877-1882. doi:10.1002/ijc.23716.

18. Joehlin-Price AS, Stephens JA, Zhang J, Backes FJ, Cohn DE, Suarez AA. Endometrial cancer insulin-like growth factor 1 receptor (IGF1R) expression increases body mass index and is associated with pathological extent and prognosis. *Cancer Epidemiol Biomarkers Prev*. 2015;25(3):438-445. doi:10.1158/1055-9965.EPI-15-1145.

19. Arem H, Park Y, Pelser C, et al. Prediagnosis body mass index, physical activity, and mortality in endometrial cancer patients. *J Natl Cancer Inst*. 2013;105:342-349. doi:10.1093/jnci/djs530.

20. Lee AH, Su D, Pasalich M, Wong YL, Binns CW. Habitual physical activity reduces risk of ovarian cancer: a case-control study in southern China. *Prev Med*. 2013;57:S31-S33. doi:10.1016/j.ypmed.2012.11.009.

21. Moorman PG, Jones LW, Akushevich L, Schildkraut JM. Recreational physical activity and ovarian cancer risk and survival. *Ann Epidemiol*. 2011;21:178-187. doi:10.1016/j.annepidem.2010.10.014.

22. Chionh F, Baglietto L, Krishnan K, et al. Physical activity, body size and composition, and risk of ovarian cancer. *Cancer Causes Control*. 2010;21:2183-2194. doi:10.1007/s10552-010-9638-y.

23. Cannioto RA, Moysich KB. Epithelial ovarian cancer and recreational physical activity: a review of epidemiological literature and implications for exercise prescription. *Gynecol Oncol*. 2015;137:559-573. doi:10.1016/j.ygyno.2015.03.016.

24. Hackshaw-McGeagh LE, Perry RE, Leach VA, et al. A systematic review of dietary, nutritional, and physical activity interventions for the prevention of prostate cancer progression and mortality. *Cancer Causes Control*. 2015;26:1521-1550. doi:10.1007/s10552-015-0659-4.

25. Liu YP, Hu FL, Li DD, et al. Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis. *Euro Urol*. 2011;60:1029-1044. doi:10.1016/j.eururo.2011.07.007.

26. Moore SC, Peters TM, Ahn J, et al. Age-specific physical activity and prostate cancer risk among white men and black men. *Cancer*. 2009;115:5060-70. doi:10.1002/cncr.24538.

27. Park SY, Haiman CA, Cheng I, et al. Racial/ethnic differences in lifestyle-related factors and prostate cancer risk: the Multiethnic Cohort study. *Cancer Causes Control*. 2015;26:1507-1515.

28. Kenfield SA, Stampfer MJ, Giovannucci E, Chan JM. Physical activity and survival after prostate cancer diagnosis in the Health Professionals Follow-Up study. *J Clin Oncol*. 2011;29(6):726-732. doi:10.1200/jco.2010.31.5226.

29. Zhong S, Ma T, Chen L, et al. Physical activity and risk of lung cancer: a meta-analysis. *Clin J Sport Med*. 2016;26(3):173-181. doi:10.1097/JSM.0000000000000219.

30. Buffart LM, Singh AS, van Loon E, Vermeulen HI, Brug J, Chinapaw M. Physical activity and the risk of developing lung cancer among smokers: a meta-analysis. *J Sci Med Sport*. 2014;17:67-71. doi:10.1016/j.jsams.2013.02.015.

31. Lam TK, Moore SC, Brinton LA, et al. Anthropometric measures and physical activity and the risk of lung cancer in never smokers: a prospective cohort study. *PLoS One*. 2013;8(8):e70672. doi:10.1371/journal.pone.0070672.

32. Leitzmann MF, Koebnick C, Abnet CC, et al. Prospective study of physical activity and lung cancer by histologic type in current, former, and never smokers. *Amer J Epi*. 2009;169:542-553. doi:10.1093/aje/kwn371.

33. Prorok PC, Andriole GL, Bresalier RS, et al. Design of the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial. *Cont Clin Trials*. 2000;21:273S-309S.

34. Gren L, Broski K, Childs J, et al. Recruitment methods employed in the prostate, lung, colorectal, and ovarian cancer screening trial. *Clin Trials*. 2009;6(1):52-59. doi:10.1177/1740774508100974.

35. McDonald JH. Multiple Regression. In: *Handbook of Biological Statistics*. 2nd ed. Baltimore, MA: Sparky House; 254-260.

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37. Wang Y, Jacobs EJ, Gansler T, et al. *Physical activity, sitting time and prostate cancer specific mortality: The Cancer Prevention Study II Nutrition Cohort*. Proceedings: AACR 107th Annual Meeting. 2016;76(14). doi:10.1158/1538-7445.AM2016-1736.

38. John EM, Koo J, Horn-Ross PL. Lifetime physical activity and risk of endometrial cancer. *Cancer Epidemiol Biomarkers Prev*. 2010;19(5):1276-1283. doi:10.1158/1055-9965.

39. De Pergola G, Silvestris F. Obesity as a major risk factor for cancer. *J Obes*. 2013. doi:10.1155/2013/291546.

40. Huang CJ, McAllister MJ, Slusher AL, Webb HE, Mock JT, Acevedo EO. Obesity-related oxidative stress: the impact of physical activity and diet manipulation. *Sport Med Open*. 2015;1:32. doi:10.1186/s40798-015-0031-y.

41. Beavers KM, Ambrosius WT, Nicklas BJ, Rejeski WJ. The independent and combined effects of physical activity and weight loss on inflammatory biomarkers in overweight and obese older adults. *J Am Geriatr Soc*. 2013;61(7):1089-1094. doi:10.1111/jgs.12321.

42. Strohacker K, Carpenter KC, McFarlin BK. Consequences of weight cycling: an increase in disease risk? *Int J Exerc Sci*. 2009;2(3):191-201.

43. Thompson HJ, McTiernan A. Weight cycling and cancer: weighing the evidence of intermittent caloric restriction and cancer risk. *Cancer Prev Res* (Phila). 2011;4(11):1736-1742. doi:10.1158/1940-6207.CAPR-11-0133.

44. Sytze van Dam P, Aleman A. Insulin-like growth factor-I, cognition and brain aging. *Euro J Pharmacol*. 2004;490:87-95. doi:10.1016/j.ejphar.2004.02.047.

45. Jette M, Sidney K, Blumchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol*. 1990;13:555-565.

CHAPTER 4

EXAMINING THE ROLE OF PHYSICAL ACTIVITY ATTRIBUTES IN CANCER INCIDENCE IN INDIVIDUALS WITH A FAMILY HISTORY OF CANCER

Abstract

Increasing evidence has demonstrated that physical activity plays a role in reducing the risk for certain cancers. However, little is known about the role that physical activity may play in risk reductions for those individuals who have familial risk of cancer. The purpose of this study is to assess how specific physical activity variables, such as intensity, duration, frequency, and activity type, affect cancer incidence outcomes for breast, colorectal, and prostate cancers in individuals at varying levels of familial risk.

We assessed self-reported demographic, dietary, and physical activity data collected from participants enrolled in the Prostate, Lung, Colorectal and Ovarian Cancer screening trial. Family history of cancer for breast, colorectal, and prostate cancers were categorized into average, moderate, or strong risk categories, according to the number of first-degree relatives diagnosed and their age at diagnosis. Cox proportional hazards models were used to identify hazard ratios and 95% CIs to determine the association between physical activity variables (type, frequency, intensity, and duration) and respective cancer outcomes.

After adjusting for multiple test correction, no variables maintained significance in the analyses. Initial variables that demonstrated potential significance included a decreased risk for colorectal cancer in individuals without a family history of cancer who reported higher levels of moderate activity frequency (HR: 0.52, 95% CI: 0.30, 0.92) and duration (HR: 0.49, 95% CI: 0.28, 0.86). Prostate cancer was initially positively associated with higher levels of moderate activity frequency (HR: 1.43, 95% CI: 1.12, 1.82) and duration (HR: 1.44, 95% CI: 1.12, 1.86).

Future studies are needed to further explore the relationship between family history and preventive behaviors, such as physical activity, to identify what, if any, preventive behaviors may affect cancer incidence in these at-risk individuals. Tailored, evidence-based recommendations are most likely an important component of behavior change and adherence.

Introduction

Inherited mutations in genes such as *BRCA1, BRCA2*, and mismatch repair genes associated with hereditary non-polyposis colorectal cancer (HNPCC), contribute to an estimated 5-10% of all cancers. However, individuals with a family history of cancer, particularly individuals with first-degree relatives (such as a sibling, parent, or child) who were diagnosed with cancer are also at an increased risk of developing cancer, even if particular genetic mutations are not identified.[1] Recommendations for individuals at increased genetic or familial risk for cancer usually include screening starting at an earlier age, more frequent screenings, preventive surgery, and chemoprevention.[2] However, individuals with a familial or genetic risk for cancer are often also interested in whether their risk can be mitigated by improving lifestyle behaviors, such as physical activity.[3]

A growing body of evidence supports the role of physical activity in the prevention of certain cancers, particularly breast, colorectal, lung, and endometrial cancers, and lesser evidence supporting reduction of risk of other cancers, such as ovarian and gastric cancer.[4] However, these risk reductions have generally been identified in populations at average risk for cancer. Few studies have examined the role of physical activity in the prevention of cancers in those at increased hereditary risk, and to our knowledge, none have examined it in individuals at increased familial risk. Studying individuals with familial risk presents a unique opportunity to assess the interaction between genetic, environmental, and behavioral factors in cancer risk. Assessing the role of lifestyle behaviors, such as physical activity, in those at familial risk is important, as they can generate specific recommendations for these individuals. Previous research has shown that while individuals at increased familial risk are not generally more likely to engage in preventive behaviors than those who are not at risk, the likelihood of adopting healthy behaviors increases when tailored information is available.[5]

A few studies have examined the role of physical activity in individuals with *BRCA1* and *BRCA2* mutations, and with *HNPCC* (Lynch Syndrome). However, results from these studies have been mixed. A systematic review by Pettapiece-Phillips et al.[6] on women with *BRCA* mutations found that physical activity may improve incidence outcomes in *BRCA1* carriers, but not *BRCA2* carriers. Research conducted on an Ashkenazi Jewish cohort found that breast cancer onset was significantly delayed in women who reported being physically active in adolescence.[7] A retrospective cohort study conducted by Pijpe et al. [8] found risk reductions for carriers of *BRCA1* and *2* mutations who participated in sports as adults (HR: 0.72, 95% CI: 0.54, 0.96) compared to those who did not, but results were inconclusive for specific activities, such as frequency of walking, cycling, or total physical activity reported.

The evidence around genetic risk for colorectal cancer and physical activity is sparse. The only study we could locate that examined the role of physical activity in hereditary colorectal cancer was conducted by Kamiza et al.[9] on Taiwanese individuals with *MLH1* and *MSH2* germline mutations. Individuals in the cohort who performed regular physical activity had a decreased risk for colorectal cancer (HR: 0.62, 95% CI: 0.41, 0.88) compared to those who did not.

It is important to note that the existing research around physical activity and hereditary cancers has only been conducted on individuals with known genetic mutations, not individuals whose increased risk was identified specifically based on family history. Yet, individuals with a family history of cancer are at a substantially increased risk of developing cancer themselves. For example, though there is no known genetic mutation that predisposes men to prostate cancer, men with a father or brother with prostate cancer have an increased risk (HR: 1.6, 95% CI: 1.24, 2.14), compared to those who do not.[10] Individuals at familial risk represent an important at-risk subpopulation for prevention research. Yet, to our knowledge, no research has been conducted on the role of physical activity in individuals whose family history suggests a moderate-to-high risk of genetic or hereditary cancer. Additionally, the majority of research conducted on these individuals has not examined whether specific attributes of physical activity (e.g., intensity, duration, frequency) affect cancer risk.

The current study examines how specific physical activity attributes affect both site-specific and overall cancer incidence in individuals at different levels of hereditary risk for breast, colorectal, and prostate cancers. Such research is a first attempt at addressing a significant gap in the literature, as it focuses on preventive factors for individuals at familial risk, as well as attempts to identify specific attributes of physical activity that affect their risk.

Methods

Participants

Eligible participants for this analysis included individuals who were participating in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer screening trial, a randomized controlled trial that was conducted between 1993 and 2013.[11] While in the PLCO trial, participants were asked to complete several self-administered questionnaires that asked about personal and family history of diseases, specifically cancers. Individuals also answered demographic, dietary, and lifestyle questions, including a supplemental questionnaire (SQX) administered in 2006, which included in-depth questions about physical activity. Participants from the PLCO trial were eligible for inclusion into the current analyses if they were cancer free prior to the administration of the SQX, and if they had completed baseline, dietary, and SQX questionnaires and had follow-up through the completion of the study (2013). To create our dataset, we included demographic, dietary, and health variables from the various PLCO surveys, including the baseline survey, dietary survey, and SQX surveys. For variables, such as incidence of diseases that were assessed more than once, we used the most recent responses. For variables known to change over time, such as smoking status, we compared answers across surveys to ensure validity of categorizations.

Family History of Cancer

Eligible participants were categorized by familial risk of cancer in two separate ways. First, we were interested in determining whether physical activity in individuals with a family history of a particular cancer (breast, colorectal, ovarian, prostate) affected the risk of that specific cancer. As we were focused on individuals with familial risk, we categorized participants by self-reported family history of cancer using established risk categorization criteria for each specific cancer (see Figure 4.1 for risk categorizations). As individuals only reported familial cancers in their first-degree relatives (parents/siblings/children) in the PLCO questionnaires, we were only able to create risk categorizations according to known cancers in these relatives.

For breast and ovarian cancers, we created four risk categorizations: 1) those without a known family history of breast or ovarian cancer (average familial risk), 2) those with one first-degree relative diagnosed with breast or ovarian cancer diagnosed at any age (moderate familial risk), 3) those with two or more first-degree relatives diagnosed with breast or ovarian cancer over age 50 (high familial risk), and 4) those with two or more first-degree relatives diagnosed with breast or ovarian cancer, at least one of whom was under age 50 (very high familial risk). We disaggregated by age of diagnosis because cancers diagnosed at a younger age are more likely to be due to a genetic mutation than those diagnosed at older ages.[12,13] Our decision to include relatives also diagnosed with ovarian cancer in breast cancer risk categorization was because mutations in breast cancer genes *BRCA1* and *BRCA2* also increase the risk of ovarian cancer.[14]

For prostate cancer, our risk categorizations included: 1) those without a known family history of prostate cancer (average familial risk), 2) those with one first-degree

Family History of Cancer	Risk Category
Breast or Ovarian Cancer	
No first-degree relatives diagnosed with breast or ovarian cancer	Average
One first-degree relative diagnosed with breast or ovarian cancer at any age	Moderate
Two or more first-degree relatives diagnosed with breast or ovarian cancer after age 50	Strong
Two or more first-degree relatives diagnosed with breast or ovarian cancer, at least one of whom was diagnosed before age 50	Very strong
Prostate Cancer	
No first-degree relatives diagnosed with prostate cancer	Average
One first-degree relative diagnosed with prostate cancer at any age	Moderate
Two or more first-degree relatives diagnosed with prostate cancer	Strong [b]
General Cancer History	
No first-degree relatives diagnosed with any cancer	Average
One first-degree relative diagnosed with any cancer at any age	Moderate
Two or more first-degree relatives diagnosed with any cancer after age 50	Strong
Two or more first-degree relatives diagnosed with any cancer, at least one of whom was diagnosed before age 50	Very strong

Figure 4.1. Familial Risk Categorizations. Risk categorizations according to categorizations for risk developed by the American Cancer Society: http://www.cancer.org/cancer/cancercauses/geneticsandcancer/heredity-and-cancer. Due to sample size restrictions, it was not possible to disaggregate strong and very strong risk groups.

relative diagnosed with prostate cancer at any age (moderate familial risk), and 3) those with two or more first-degree relatives diagnosed with prostate cancer, including those diagnosed under age 60 (categorizations of high and very high familial risk were limited due to sample size).

We did not have sufficient sample size to examine cancer outcomes in individuals who reported a family history of colorectal cancer.

Finally, we were also interested in examining the role of physical activity in individuals who had a family history of cancer in general. For breast, colorectal, and prostate cancer outcomes, we separated individuals into the following categories: 1) those without a known family history of any cancer (average familial risk), 2) those with one first-degree relative diagnosed with cancer (moderate familial risk), 3) those with two or more first-degree relatives diagnosed with any cancer over age 50 (high familial risk), and 4) those with two or more first-degree relatives diagnosed with any cancer, at least one of whom was diagnosed under age 50 (very high familial risk).

Physical Activity Variables

We were interested in examining specific physical activity variables, including frequency, type, intensity, and duration.

Type

To calculate type, we aggregated individual activity variables (e.g., running, swimming, weight lifting) collected in the SQX into composite activity types (aerobic/strength). Activity types were categorized using NIH categorizations.[15]

Frequency

To assess frequency, we then added all self-reported weekly frequency of specific activities within these categories (e.g., dancing (2x/week) + jogging (1x/week) = 3 aerobic activities per week) for total weekly frequency scores of aerobic and strength-based activities. We also created an overall composite of weekly frequency of all physical activity.

Intensity/Duration

Intensity and duration variables were initially collected in the SQX and were assessed separately. For strenuous exercise, individuals were asked to assess, "on average, how many days per week did you spend in any physical activity strenuous enough to work up a sweat or increase breathing and heart rate to very high levels?" For moderate exercise, individuals were asked to assess, "on average, how many days per week did you spend in any moderate physical activity where you worked up a light sweat or increased your breathing and heart rate to moderate levels?" Individuals were then asked to assess the average duration of each strenuous or moderate session.

Proportion

We also looked at the proportion of time spent in a particular type of activity (aerobic/strength). Physical activity guidelines generally recommend that individuals engage in both aerobic and strength-based activities (CDC PA guidelines)[16]; we were interested in understanding whether individuals who spend a higher percentage of time in a specific activity mode (e.g., a man who only engages in weight lifting) developed different types of cancer than those with a more even ratio. To assess this, we created two ratio variables that identified the proportion of time spent in either mode of physical activity (e.g., frequency of aerobic activity/ total frequency of all activities = proportion of time spent in aerobic activity).

Statistical Analyses

We conducted separate analyses for each cancer outcome, specifically breast, ovarian, colorectal, and prostate cancers. Breast, ovarian, and prostate cancers are all sex-specific cancers (we did not include male breast cancer); however, for colorectal cancer, we combined male and female colorectal cancers in our outcome, as our sample size was too small to stratify on sex. We conducted univariate analyses of potential confounding variables identified from existing literature and included variables that were identified as confounders in the literature or were statistically significant in our univariate analyses. We also conducted sensitivity analyses to assess for the effects of large variation among the physical activity variables.

We then conducted multivariate Cox proportional hazard regression models, with site-specific cancer incidence as the dependent variable. We analyzed each physical activity variable (type, frequency, intensity, duration, proportion) to assess its impact on the separate cancer incidence outcomes (breast, colorectal, ovarian, prostate). Follow-up time was defined as the time between completion of the SQX questionnaire until cancer diagnosis, or through 2013. Finally, we applied the Benjamini-Hochberg procedure for multiple test correction, using a false discovery rate of 0.10 for all findings.[17] All analyses were conducted using Stata 12.0. This study was approved by the Institutional Review Board of the University of Utah.

Results

Table 4.1 provides demographic information on individuals included in our analyses by their respective cancer outcomes. Tables 4.2–4.6 provide specific findings for family history and specific cancer outcomes. After applying the procedure for multiple test correction, no variables maintained significance in the analyses. Physical activity variables were not associated with an increased or decreased risk in individuals with high familial risk (2 or more first-degree relatives diagnosed with cancer) for specific or for any cancers.

No effects of family history appeared in individuals with a diagnosis of colorectal cancer. Increased moderate activity frequency (HR: 0.52, 95% CI: 0.30, 0.92) and duration (HR: 0.49, 95% CI: 0.28, 0.86) were associated with a decreased risk of colorectal cancer in individuals without a family history of cancer, though these did not maintain significance after adjusting for multiple test correction.

Most findings demonstrated an increase in cancer incidence commensurate with an increase in physical activity. Initial variables demonstrating significance prior to multiple test correction tended to indicate effect in individuals at a moderate familial risk for specific cancer (i.e., having one first-degree relative diagnosed over age 50). For example, strength-training frequency was marginally associated with an increased risk for breast cancers in individuals with a moderate family history of any type of cancer (HR: 1.10, 95% CI: 0.99, 1.22). Increased strenuous activity frequency (HR: 1.43, 95% CI: 1.12, 1.82) and duration (HR: 1.44, 95% CI: 1.12, 1.86) were also associated with higher risks of prostate cancer in individuals with a moderate family history of any cancer.

Table 4.1. Demographic Characteristics of Individuals in the Prostate, Lung, Colorectal, and Ovarian Cancer Trial, by Cancer Outcome

Variable	No cancer (n = 38,736)	Cancer diagnosis (n = 645)
Breast cancer outcomes		
Mean age at study enrollment	61.8	61.7
Race		
Non-Hispanic white	89.4%	90.4%
Other	10.6%	9.6%
Average Body Mass Index (BMI) at SQX	27.0	27.9
Average daily servings of fruit	2.8	2.6
Average daily serving of vegetables	3.8	3.7
Average number of alcoholic drinks per day	0.40	0.47
Smoking status at SQX		
Never smoked	56.5%	55.8%
Current smoker	5.9%	5.9%
Former smoker	37.6%	38.3%
Average smoking pack years	12.3	14.5
Family history of any cancer at SQX[a]		
0	34.8%	30.2%
1	33.8%	32.3%
2+	19.9%	22.9%
2+ <50	11.5%	14.7%
Family history of breast or ovarian cancer at SQX[a,b]		
0	79.2%	73.2%
1	17.6%	20.4%
2+	1.6%	3.2%
2+ <50	1.6%	3.2%
Colorectal Cancer Outcomes	(n=74,692)	(n=209)
Mean age at study enrollment	61.8	63.4
Race		
Non-Hispanic white	89.1%	87.6%
Other	10.9%	12.4%
Average Body Mass Index (BMI) at SQX	27.3	28.9
Average daily servings of fruit	2.7	2.8

Table 4.1 continued

Variable	No cancer (n = 38,736)	Cancer diagnosis (n = 645)
Average daily serving of vegetables	3.9	4.1
Average number of alcoholic drinks per day	0.78	0.78
Smoking status at SQX		
Never smoked	46.9%	44.4%
Current smoker	6.2%	5.1%
Former smoker	46.9%	50.5%
Average smoking pack years	17.8	22.3
Family history of any cancer at SQX[a]		
0	38.5%	38.3%
1	33.4%	34.4%
2+	18.3%	16.7%
2+ <50	9.7%	10.5%
Family history of colorectal cancer at SQX[a]		
0	89.4%	90.4%
1	9.3%	7.7%
2+	<1%	1.9%
2+ <50	<1%	0.0%
Prostate Cancer Outcomes	(n=34,645)	(n=1083)
Mean age at study enrollment	61.7	61.2
Race		
Non-Hispanic white	88.7%	88.8%
Other	11.3%	11.2%
Average Body Mass Index (BMI) at SQX	27.7	27.5
Average daily servings of fruit	2.6	2.5
Average daily serving of vegetables	4.0	3.8
Average number of alcoholic drinks per day	1.22	1.23
Smoking status at SQX		
Never smoked	35.9%	39.7%
Current smoker	6.6%	6.2%
Former smoker	57.5%	54.1%
Average smoking pack years	24.3	21.3

Table 4.1 continued

Variable	No cancer (n = 38,736)	Cancer diagnosis (n = 645)
Family history of any cancer at SQX		
0	42.7%	41.9%
1	33.0%	32.7%
2+	16.5%	15.7%
2+ <50	7.8%	9.7%
Family history of prostate cancer at SQX[c]		
0	91.3%	88.2%
1	7.9%	10.7%
2+	<1%	<1%
2+ <60	<1%	<1%

Note. SQX: Supplemental Questionnaire (administered in 2006-2007)

[a] Family History outcomes: 0 = No first-degree relatives diagnosed with cancer; 1= One first-degree relative diagnosed with cancer over age 50, 2+ = Two or more first-degree relatives diagnosed with cancer over age 50; 2+ <50 = Two or more first-degree relatives diagnosed with cancer, at least one of whom was diagnosed under age 50.

[b] Having a family history of either breast or ovarian cancer was considered for breast cancer outcomes, given the strong relationship between ovarian cancer and genetic risk for breast cancers.

[c] In the case of prostate cancer, categorizations remain the same, except that first-degree relatives were considered to have a "young" diagnosis if they were diagnosed with prostate cancer before age 60.

Table 4.2. Examining Exercise Variables by Familial History of Breast & Ovarian Cancer: Breast Cancer Outcome in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial[a]

	No FH		1 Dx		2+ Dx		2+ Dx, <50	
Type of physical activity	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Total weekly aerobic activity[b] frequency	0.98 (0.91, 1.06)	0.75	0.98 (0.84, 1.14)	0.80	1.27 (0.85, 1.74)	0.28	0.86 (0.51, 1.44)	0.57
Total weekly strength training[c] frequency	1.06 (0.99, 1.14)	0.06	0.96 (0.83, 1.11)	0.61	1.04 (0.72, 1.53)	0.80	0.92 (0.54, 1.57)	0.77
Total frequency of all activities per week	1.02 (0.97, 1.07)	0.29	0.97 (0.88, 1.07)	0.63	1.10 (0.87, 1.41)	0.40	0.90 (0.64, 1.27)	0.57
Ratio of aerobic activity over all activity per week	0.75 (0.54, 1.04)	0.08	0.73 (0.37, 1.43)	0.36	1.64 (0.25, 10.51)	0.59	1.39 (0.19, 10.14)	0.74
Ratio of strength training activity over all activity per week	1.34 (0.95, 1.89)	0.09	1.54 (0.74, 3.18)	0.24	0.51 (0.08, 3.00)	0.46	0.58 (0.08, 4.14)	0.58
Total frequency of strenuous activity per week								
< 2 sessions per week	Ref		Ref		Ref		Ref	
>2 sessions per week	0.99 (0.79, 1.22)	0.93	1.07 (0.69, 1.64)	0.75	2.39 (0.81. 7.05)	0.11	0.80 (0.20, 3.22)	0.76
Average duration of strenuous activity session								
<30 minutes	Ref		Ref		Ref		Ref	
>30 minutes	1.01 (0.81, 1.25)	0.90	1.24 (0.80, 1.92)	0.32	2.23 (0.74, 6.75)	0.15	1.50 (0.42, 5.25)	0.14
Total frequency of moderate activity per week								
<2 sessions per week	Ref		Ref		Ref		Ref	
>2 sessions per week	1.07 (0.88, 1.35)	0.54	0.75 (0.48, 1.18)	0.22	1.24 (0.41, 3.77)	0.70	0.50 (0.12, 1.99)	0.33
Average duration of moderate activity session								
<30 minutes	Ref		Ref		Ref		Ref	
>30 minutes	0.98 (0.78, 1.25)	0.93	0.91 (0.57, 1.46)	0.72	3.29 (0.82, 13.10)	0.09	0.32 (0.85, 1.22)	0.85

Note. FH: Family history; 1 Dx: One first-degree family member diagnosed with breast or ovarian cancer at any age; 2+ Dx: Two or more first-degree family members diagnosed with breast or ovarian cancer, over the age of 50; 2+ Dx <50: Two or more first-degree family members diagnosed with breast or ovarian cancer, at least one of whom was diagnosed under the age of 50.

[a] Models are adjusted on: age, race, age at first menstruation, age at menarche, number of pregnancies, birth control use (ever/never), Body Mass Index (BMI), hormone replacement therapy status (current/ever/never), family history of cancer, number of servings of fruit and vegetables eaten per day, number of alcoholic drinks per day, hormone replacement therapy status (ever/never/former), smoking status (ever/never/former), and smoking pack years.

[b] Aerobic activities included: aerobics, cycling, jogging, swimming, dancing, and walking one mile without stopping.

[c] Strength training activities included: weight lifting, gardening, and calisthenics. Gardening is categorized as a strength-based activity according to the National Institutes of Health: https://www.nhlbi.nih.gov/health/health-topics/topics/phys/types

Table 4.3. Examining Exercise Variables by Any Family History of Cancer: Breast Cancer Outcomes in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial[a]

	No FH		1 Dx		2+ Dx		2+ Dx, <50	
Type of physical activity	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Total weekly aerobic activity[b] frequency	0.93 (0.85, 1.06)	0.31	1.02 (0.91, 1.14)	0.66	1.01 (0.89, 1.16)	0.79	0.97 (0.81, 1.17)	0.81
Total weekly strength training[c] frequency	0.97 (0.87, 1.09)	0.70	1.10 (0.99, 1.22)	0.05[d]	1.03 (0.91, 1.17)	0.54	1.01 (0.85, 1.18)	0.90
Total frequency of all activities per week	0.96 (0.89, 1.04)	0.37	1.05 (0.98, 1.12)	0.12	1.02 (0.94, 1.11)	0.57	0.99 (0.89, 1.11)	0.95
Ratio of aerobic activity over all activity per week	0.81 (0.48, 1.38)	0.44	0.72 (0.43, 1.21)	0.22	0.92 (0.52, 1.62)	0.78	0.63 (0.28, 1.37)	0.25
Ratio of strength training activity over all activity per week	1.27 (0.72, 2.21)	0.39	1.46 (0.86, 2.49)	0.15	1.01 (0.56, 1.82)	0.96	1.63 (0.70, 3.75)	0.25
Total frequency of strenuous activity per week								
< 2 sessions per week	Ref		Ref		Ref		Ref	
>2 sessions per week	0.82 (0.58, 1.16)	0.26	1.20 (0.86, 1.66)	0.27	1.18 (0.80, 1.72)	0.38	0.84 (0.51, 1.40)	0.52
Average duration of strenuous activity session								
<30 minutes	Ref		Ref		Ref		Ref	
>30 minutes	0.80 (0.57, 1.12)	0.20	1.28 (0.92, 1.78)	0.13	1.35 (0.92, 1.99)	0.11	0.92 (0.55, 1.51)	0.74
Total frequency of moderate activity per week								
<2 sessions per week	Ref		Ref		Ref		Ref	
>2 sessions per week	0.92 (0.65, 1.32)	0.68	1.08 (0.76, 1.54)	0.63	1.06 (0.70, 1.58)	0.77	0.82 (0.48, 1.39)	0.47
Average duration of moderate activity session								
<30 minutes	Ref		Ref		Ref		Ref	
>30 minutes	0.80 (0.56, 1.15)	0.24	0.92 (0.64, 1.32)	0.68	1.56 (0.99, 2.47)	0.06	0.75 (0.43, 1.28)	0.29

Note. FH: Family history; 1 Dx: One first-degree family member diagnosed with any cancer at any age; 2+ Dx: Two or more first-degree family members diagnosed with any cancer, over the age of 50; 2+ Dx <50: Two or more first-degree family members diagnosed with any cancer, at least one of whom was diagnosed under the age of 50.

[a] Models are adjusted on: age, race, age at first menstruation, age at menarche, number of pregnancies, birth control use (ever, never), Body Mass Index (BMI), hormone replacement therapy status (current/ever/never), family history of cancer, number of servings of fruit and vegetables eaten per day, number of alcoholic drinks per day, hormone replacement therapy status (ever, never, former), smoking status (ever, never, former), and smoking pack years.

[b] Aerobic activities included: aerobics, cycling, jogging, swimming, dancing, and walking one mile without stopping.

[c] Strength training activities included: weight lifting, gardening, and calisthenics. Gardening is categorized as a strength-based activity according to the National Institutes of Health: https://www.nhlbi.nih.gov/health/health-topics/topics/phys/types

[d] After applying the Benjamini-Hochberg procedure for multiple test correction (false discovery rate of 0.10), these variables did not maintain significance.

Table 4.4. Examining Exercise Variables by Familial History of Prostate Cancer: Prostate Cancer Outcomes in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial[a]

	No FH		1 Dx		2+ Dx & young combined	
Type of physical activity	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Total weekly aerobic activity[b] frequency	1.01 (0.96, 1.06)	0.62	0.97 (0.84, 1.13)	0.78	1.13 (0.79, 1.63)	0.48
Total weekly strength training[c] frequency	1.00 (0.95, 1.04)	0.99	1.04 (0.92, 1.19)	0.47	0.96 (0.67, 1.38)	0.85
Total frequency of all activities per week	1.00 (0.97, 1.03)	0.77	1.01 (0.93, 1.10)	0.75	1.03 (0.81, 1.30)	0.77
Ratio of aerobic activity over all activity per week	1.02 (0.81, 1.28)	0.82	0.57 (0.28, 1.18)	0.13	2.87 (0.39, 20.8)	0.29
Ratio of strength training activity over all activity per week	1.13 (0.88, 1.45)	0.31	1.53 (0.72, 3.25)	0.26	0.21 (0.03, 1.39)	0.10
Total frequency of strenuous activity per week						
< 2 sessions per week	Ref		Ref		Ref	
>2 sessions per week	1.25 (0.97, 1.30)	0.112	1.36 (0.89, 2.08)	0.14	1.42 (0.35, 5.79)	0.62
Average duration of strenuous activity session						
<30 minutes	Ref		Ref		Ref	
>30 minutes	1.07 (0.92, 1.24)	0.36	1.31 (0.84, 2.04)	0.22	1.97 (0.38, 9.97)	0.41
Total frequency of moderate activity per week						
<2 sessions per week	Ref		Ref		Ref	
>2 sessions per week	1.24 (1.05, 1.46)	0.01	1.04 (0.65, 1.66)	0.85	0.37 (0.08, 1.67)	0.19
Average duration of moderate activity session						
<30 minutes	Ref		Ref		Ref	
>30 minutes	1.10 (0.93, 1.30)	0.24	1.20 (0.72, 1.99)	0.47	0.48 (0.08, 2.76)	0.42

Note. FH: Family history; 1 Dx: One first-degree family member diagnosed with prostate cancer at any age; 2+ Dx & Young Combined: Two or more first-degree relatives diagnosed with prostate cancer at any age, including under age 60.

[a] Models are adjusted on: age, race, Body Mass Index (BMI), family history of cancer, number of servings of fruit and vegetables eaten per day, number of alcoholic drinks per day, smoking status (ever/never/former), and smoking pack years.

[b] Aerobic activities included: aerobics, cycling, jogging, swimming, dancing, and walking one mile without stopping.

[c] Strength training activities included: weight lifting, gardening, and calisthenics. Gardening is categorized as a strength-based activity according to the National Institutes of Health: https://www.nhlbi.nih.gov/health/health-topics/topics/phys/types

Table 4.5. Examining Exercise Variables by Any Family History of Cancer: Prostate Cancer Outcomes in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial[a]

	No FH		1 Dx		2+ Dx		2+ Dx, <60	
Type of physical activity	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Total weekly aerobic activity[b] frequency	1.04 (0.97, 1.11)	0.25	1.00 (0.92, 1.09)	0.87	0.96 (0.85, 1.09)	0.60	0.95 (0.80, 1.12)	0.55
Total weekly strength training[c] frequency	0.97 (0.90, 1.04)	0.42	1.04 (0.97, 1.12)	0.21	0.98 (0.88, 1.09)	0.80	1.01 (0.88, 1.15)	0.85
Total frequency of all activities per week	1.00 (0.96, 1.04)	0.88	1.02 (0.97, 1.07)	0.36	0.98 (0.91, 1.05)	0.64	0.98 (0.90, 1.08)	0.82
Ratio of aerobic activity over all activity per week	1.17 (0.84, 1.63)	0.33	0.84 (0.58, 1.22)	0.37	1.04 (0.60, 1.78)	0.88	0.67 (0.32, 1.43)	0.31
Ratio of strength training activity over all activity per week	1.07 (0.74, 1.54)	0.69	1.09 (0.74, 1.62)	0.64	1.34 (0.72, 2.48)	0.34	1.37 (0.61, 3.05)	0.43
Total frequency of strenuous activity per week								
< 2 sessions per week	Ref		Ref		Ref		Ref	
>2 sessions per week	1.01 (0.81, 1.25)	0.90	1.43 (1.12, 1.82)	<0.01[d]	1.09 (0.77, 1.54)	0.61	0.98 (0.64, 1.49)	0.93
Average duration of strenuous activity session								
<30 minutes	Ref		Ref		Ref		Ref	
>30 minutes	0.90 (0.72, 1,11)	0.34	1.44 (1.12, 1.86)	<0.01[d]	1.16 (0.81, 1.66)	0.40	0.88 (0.57, 1.37)	0.59
Total frequency of moderate activity per week								
<2 sessions per week	Ref		Ref		Ref		Ref	
>2 sessions per week	1.38 (1.07, 1.76)	0.01[d]	1.15 (0.88, 1.49)	0.29	1.04 (0.71, 1.52)	0.83	1.00 (0.62, 1.62)	0.97
Average duration of moderate activity session								
<30 minutes	Ref		Ref		Ref		Ref	
>30 minutes	1.00 (0.79, 1.28)	0.94	1.22 (0.92, 1.62)	0.15	1.40 (0.91, 2.15)	0.12	0.82 (0.51, 1.33)	0.43

Note. FH: Family history; 1 Dx: One first-degree family member diagnosed with any cancer at any age; 2+ Dx: Two or more first-degree relatives diagnosed with any cancer at over age 50; 2+ Dx <60: Two or more first-degree relatives diagnosed with any cancer, at least one of whom was diagnosed under age 50 or 60, if the cancer was prostate cancer.

[a] Models are adjusted on: age, race, Body Mass Index (BMI), family history of cancer, number of servings of fruit and vegetables eaten per day, number of alcoholic drinks per day, smoking status (ever/never/former), and smoking pack years.

[b] Aerobic activities included: aerobics, cycling, jogging, swimming, dancing, and walking one mile without stopping.

[c] Strength training activities included: weight lifting, gardening, and calisthenics. Gardening is categorized as a strength-based activity according to the National Institutes of Health: https://www.nhlbi.nih.gov/health/health-topics/topics/phys/types

[d] After applying the Benjamini-Hochberg procedure for multiple test correction (false discovery rate of 0.10), these variables did not maintain significance.

Table 4.6. Examining Exercise Variables by Any Family History of Cancer: Colorectal Cancer Outcomes in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial[a]

	No FH		1 Dx		2+ Dx		2+ Dx, <50	
Type of physical activity	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Total weekly aerobic activity[b] frequency	0.91 (0.74, 1.13)	0.43	1.05 (0.88, 1.26)	0.53	0.97 (0.75, 1.26)	0.85	0.86 (0.59, 1.25)	0.43
Total weekly strength training[c] frequency	0.95 (0.79, 1.14)	0.63	1.03 (0.87, 1.22)	0.67	1.07 (0.81, 1.42)	0.58	1.13 (0.92, 1.41)	0.23
Total frequency of all activities per week	0.95 (0.84, 1.07)	0.43	1.03 (0.93, 1.15)	0.51	1.05 (0.91, 1.21)	0.50	0.98 (0.81, 1.19)	0.90
Ratio of aerobic activity over all activity per week	0.65 (0.27, 1.55)	0.33	0.90 (0.40, 2.02)	0.80	1.00 (0.32, 3.06)	0.99	0.36 (0.08, 1.65)	0.19
Ratio of strength training activity over all activity per week	1.55 (0.62, 3.87)	0.34	0.95 (0.41, 2.15)	0.90	0.86 (0.28, 2.63)	0.79	1.79 (0.39, 8.04)	0.44
Total frequency of strenuous activity per week								
< 2 sessions per week	Ref		Ref		Ref		Ref	
>2 sessions per week	0.95 (0.54, 1.66)	0.85	1.12 (0.66, 1.91)	0.66	0.70 (0.33, 1.46)	0.34	1.14 (0.47, 2.74)	0.75
Average duration of strenuous activity session								
<30 minutes	Ref		Ref		Ref		Ref	
>30 minutes	0.63 (0.35, 1.11)	0.11	1.01 (0.59, 1.72)	0.96	0.55 (0.26, 1.15)	0.11	1.12 (0.46, 2.71)	0.80
Total frequency of moderate activity per week								
<2 sessions per week	Ref		Ref		Ref		Ref	
>2 sessions per week	0.52 (0.30, 0.92)	0.03[d]	1.09 (0.61, 1.92)	0.76	1.18 (0.54, 2.55)	0.66	0.60 (0.24, 1.46)	0.26
Average duration of moderate activity session								
<30 minutes	Ref		Ref		Ref		Ref	
>30 minutes	0.49 (0.28, 0.86)	0.01[d]	1.15 (0.63, 2.08)	0.64	0.95 (0.43, 2.06)	0.90	0.94 (0.51, 1.73)	0.86

Note. FH: Family history; 1 Dx: One first-degree family member diagnosed with any cancer at any age; 2+ Dx: Two or more first-degree relatives diagnosed with any cancer at over age 50; 2+ Dx <50: Two or more first-degree relatives diagnosed with any cancer, at least one of whom was diagnosed under age 50.

[a] Models are adjusted on: age, sex, race, Body Mass Index (BMI), hormone replacement therapy status (current, ever, never), family history of cancer, number of servings of fruit and vegetables eaten per day, number of alcoholic drinks per day, smoking status (ever/never/former), and smoking pack years.

[b] Aerobic activities included: aerobics, cycling, jogging, swimming, dancing, and walking one mile without stopping.

[c] Strength training activities included: weight lifting, gardening, and calisthenics. Gardening is categorized as a strength-based activity according to the National Institutes of Health: https://www.nhlbi.nih.gov/health/health-topics/topics/phys/types

[d] After applying the Benjamini-Hochberg procedure for multiple test correction (false discovery rate of 0.10), these variables did not maintain significance.

Discussion

Our findings, while not statistically significant, still add to the growing body of literature examining the relationship between physical activity and cancer outcomes. Individuals at increased family history of cancer often express interest in engaging in preventive behaviors, including diet and lifestyle modifications, which they can undertake to reduce their risk.[3] Current evidence suggests that, while there may be preventive actions that all individuals can take to mitigate their risk of cancer, individuals with a family history of cancer do not appear to reduce their risk of cancer through increased physical activity. In fact, the only reduced risk we identified, though nonsignificant after multiple test correction, was in individuals without any family history of cancer, which aligns with previously published research around the benefits of physical activity and risk for colorectal cancer.[18]

In our study, physical activity appeared to increase the risk of certain cancers, including breast and prostate cancers, in individuals with a moderate family history of cancer. This finding is likely spurious, however, given the nonlinear dose-response relationship in the findings. Nonetheless, as very little research has been published on this topic, it is important that future research continue to examine the role of physical activity in individuals at increased risk for cancer, with an eye toward specifically identifying attributes of physical activity (such as intensity or duration) that may improve cancer risk in these higher risk subgroups. There may be aspects of both familial history and physical activity that affect the relationship. For example, individuals with a family history of cancer may be more motivated to both participate in healthy lifestyle behaviors, and undergo cancer screening. Recent pooled analyses of 1.44 million Americans determined that increased leisure time activity was associated with an increased risk of prostate cancer in men with unspecified family history, which the authors suggested may be due to the fact that highly active men are more likely to obtain prostate screening than inactive men.[4] Research has not yet demonstrated that those individuals who receive standard family history risk messages are more likely to change their lifestyle behaviors[5]; however, it is possible that participating in a cancer screening trial did affect both lifestyle and screening (and thus, earlier detection). It is also possible, as has been suggested, that physical activity may be associated with reduced mortality of cancers that are identified. We did not have sufficient power to analyze the effect of physical activity on cancer mortality. Future studies assessing how physical activity impacts cancer risk in individuals with a family history should attempt to determine the continuity of health behaviors over time, to further study the interaction between lifestyle and screening behaviors.

Limitations

There were several limitations to this study. All family history was self-reported, which may have resulted in underreporting of cancer, though the limitation to first-degree relatives may make this less likely than if all family history were being reported.[19-21] Similarly, all physical activity variables were self-reported as well, which may have resulted in over-reporting of physical activity, as has been demonstrated in previous studies.[22] Additionally, the categorical nature of the duration and intensity questions prevented their combination, which would have allowed us to provide a more standard metric, such as METs.[23] The lack of standardized variables limits the generalizability of the data. Future research is needed to assess how standard physical activity variables can be applied to individuals with a confirmed family history.

Conclusion

As the evidence of the beneficial role of physical activity in the prevention of cancer continues to accumulate, it is important to examine the mechanisms that are involved in this protective effect. Such research could inform preventive recommendations for individuals who are at an increased genetic risk for cancers, who often seek behavioral and lifestyle changes as a way to mitigate their perceived risk. As of yet, the evidence around the benefits of physical activity to these individuals is limited. Further research is needed to delineate the effect of various types and durations of physical activity on risk for cancer in individuals at low, moderate, and high familial and genetic risks.

References

1. Turati F, Edefonti V, Bosetti C, et al. Family history of cancer and the risk of cancer: a network of case-control studies. *Ann Oncol*. 2013;00:1-6. doi:10.1093/annonc/mdt280.

2. Riley BD, Culver JO, Skrzynia C, et al. Essential elements of genetic cancer risk assessment, counseling, and testing: updated recommendations of the National Society of Genetic Counselors. *J Genet Counsel*. 2012;21:151-161. doi:10.1007/s10897-011-9462-x.

3. Howell LA, Brockman TA, Sinicrope PS, et al. Receptivity and preferences in cancer risk reduction lifestyle programs: a survey of colorectal cancer family members. *J Behav Health*. 2013;2(4):279-290. doi:10.5455/jbh.20130921013627.

4. Moore SC, Lee I, Weiderpass E, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA Intern Med*. 2016. doi:10.1001/jamainternmed.2016.1548.

5. Claasen L, Henneman L, Janssens AC, et al. Using family history information to promote healthy lifestyles and prevent diseases; a discussion of the evidence. *BMC Public Health*. 2010;10:248. doi:10.1186/1471-2458-10-248.

6. Pettapiece-Phillips R, Narod SA, Kotsopoulos J. The role of body size and physical activity on the risk of breast cancer in BRCA mutation carriers. *Cancer Causes Control*. 2015;26:333-344. doi:10.1007/s10552-014-0521-0.

7. King MC, Marks JH, Handell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science*. 2003;302:643-646.

8. Pijpe A, Manders P, Brohet R, et al. Physical activity and the risk of breast cancer in BRCA1/2 mutation carriers. *Breast Cancer Res Treat*. 2010;120:235-244. doi:10.1007/s10549-009-0476-0.

9. Kamiza AB, Hsieh LL, Tang R, et al. Risk factors associated with colorectal cancer in a subset of patients with mutations in MLH1 and MSH2 in Taiwan fulfilling the Amsterdam II criteria for Lynch syndrome. *PLoS ONE*. 2015;10(6):e0130018. doi:10.1371/journal.pone.0130018.

10. Randazzo M, Muller A, Carlsson S, et al. A positive family history as a risk factor for prostate cancer in a population-based study with organized prostate-specific antigen screening: results of the Swiss European Randomised Study of Screening for Prostate Cancer (ERSPC, Aarau). *BJU Int*. 2016;117:576-583. doi:10.1111/bju.13310.

11. Prorok PC, Andriole GL, Bresalier RS, et al. Design of the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial. *Contr Clin Trials*. 2000;21:273S-309S.

12. Prochazka M, Hall P, Granath F, Czene K. Family history of breast cancer and young age at diagnosis of breast cancer increase risk of second primary malignancies in women: a population-based cohort study. *Brit J Cancer*. 2006;95:1291-1295. doi:10.1038/sj.bjc.6603404.

13. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willet WC. A prospective study of family history and the risk of colorectal cancer. *New Engl J Med*. 1994;331(25):1669-1674.

14. Bergfeldt K, Nilsson B, Einhorn S, Hall P. Breast cancer risk in women with primary ovarian cancer – a case-control study. *Euro J Cancer*. 2001;37:2229-2234.

15. *Physical Activity and Your Heart*. https://www.nhlbi.nih.gov/book/export/html/4853. Accessed August 13, 2016.

16. Centers for Disease Control and Prevention. How much physical activity do older adults need? http://go4life.nia.nih.gov/. Accessed June 4, 2015.

17. McDonald JH. Multiple Regression. In: *Handbook of Biological Statistics*. 2nd ed. Baltimore, MA: Sparky House Publishing; 254-260.

18. Campbell PT, Patel AV, Newton CC, Jacobs EJ, Gapstur SM. Associations of recreational physical activity and leisure time spent sitting with colorectal cancer survival. *J Clin Oncol*. 2013;31(7):876-885. doi:10.1200/JCO.2012.45.9735.

19. Qureshi N, Wilson B, Santaguida P, et al. Collection and use of cancer family history in primary care. *Evid Rep Technol Assess* (Full Rep). 2007;159:1-84.

20. Ziogas A, Anton-Culver H. Validation of family history data in cancer family registries. *Am J Prev Med*. 2003;24(2):190-198. doi:10.1016/S0749-3797(02)00593-7.

21. King TM, Tong L, Pack RJ, Spencer C, Amos CI. Accuracy of family history of cancer as reported by men with prostate cancer. *Urology*. 2002;59:546-550.

22. Nusser SM, Beyler NK, Welk GJ, Carriquiry AL, Fuller WA, King BMN. Modeling errors in physical activity recall data. *J Phys Activ Health*. 2012;9(Suppl 1):S56-S67.

23. Jette M, Sidney K, Blumchen G. Metabolic equivalents (METs) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol*. 1990;13:555-565.

CHAPTER 5

CONCLUSIONS

Our research demonstrates the importance of further study into the relationship between physical activity, body habitus and cancer. In general, our study found that physical activity, specifically aerobic activity, was most beneficial to obese individuals, particularly women, in reducing all-cancer incidence. Due to the larger sample size in our first study, we were able to evaluate physical activity separately by stratifying participants' BMI status. In the following two studies, however, small sample sizes only allowed us to control for BMI status within analyses. This is unfortunate, but is often the reality for studies examining cancer incidence as an endpoint, given the relative rarity of cancer relative to the population being studied over a given period of time.

The findings in our studies highlight a few important challenges that should be accounted for, in future research examining physical activity and cancer incidence. First, in order to properly understand how BMI interacts with physical activity to influence cancer outcomes, future studies should disaggregate participants by BMI categories (underweight, normal, overweight, obese), as outcomes of physical activity may affect these populations very differently. The various biological mechanisms that link obesity to several cancers (metabolic disruption, increased sex hormone production, decreased leptin, increased inflammatory cytokines) are also individually linked to the risk of cancer.[1-4] Yet, as the causes of obesity are multi-factorial, disaggregating by BMI status may account for existing genetic, environmental, and medical attributes specific to obesity (e.g. metabolic disruption) that are not otherwise accounted for in cancer research.

Second, our research highlights the inherent challenges in assessing physical activity with respect to cancer. Cancers often take decades to develop, meaning that preventive behaviors, which affect rates of cancer, such as physical activity, need to be studied over the course of time. Furthermore, similar to dietary factors, the extent to which a person is physically active may change dramatically throughout the life course. Little is known about how these changes affect cancer risk, which is important, particularly as it is clear that in general, adults are less physically active as they age.[5] Future studies assessing the role of physical activity in cancer prevention can address such challenges by building standardized metrics into longitudinal cohort designs that assess known biomarkers of risk, in order to determine how and when changes to physical activity affect these intermediate outcomes (such as free estradiol levels, leptin, or IGF-1 levels) that are associated with increased cancer risk.[3,4]

Third, our research highlights the challenges of using secondary cohort data to study new questions about cancer risk. The primary purpose of the PLCO trial was to identify whether cancer screening for prostate, lung, colorectal and ovarian cancer improved cancer mortality. Although the study included some physical activity variables, these variables were largely collected at a single time point (through the SQX questionnaire which was distributed in 2006-2007), which limits their overall reliability within a longitudinal study, such as the PLCO trial. Additionally, as it was not a main focus of the study, physical activity questions that were included were not standardized around existing physical activity metrics (such as METs), which limits our ability to compare our findings with other research studies. Such limitations are inherent when using secondary data sources to look at new outcomes.

Such reminders are timely, as the rollout of the United States government's new Open Data Policy commences.[6] This policy requires that datasets generated under federally funded research be available to the public.[6] The purpose of this policy is to encourage innovation and continued use of secondary data sources, but it is important to acknowledge the inherent limitations in these data, since null or irregular findings may be a result of natural data limitations in studies that attempt to further analyze data that may not have been designed to support such outcomes. Our research highlights the importance of creating standardized selection criteria to identify appropriate datasets for further analyses. Such selection criteria for future research on the role of physical activity and cancer incidence in individuals with a family history of cancer might include: 1) ensuring physical activity variables are either already standardized to gold standard metrics (such as METs, accelerometer, etc.), or that such metrics can be calculated from existing variables; 2) selecting studies with confirmed, rather than self-reported, family history of cancers; 3) requiring that physical activity metrics are collected on an ongoing basis in longitudinal studies; and 4) selecting studies that include biomarker data.

In general, it is important to continue to accumulate more evidence around the role of physical activity in preventing cancer. A recent study of physical activity and overall mortality found that even an increase of 15 minutes of physical activity per day could extend life expectancy by 3 years.[7] As older individuals are less likely to be motivated toward physical activity by typical health behavioral strategies[8], identifying clear, attainable risk management recommendations for the minimal effective dose of physical activity needed is a realistic, important goal for this area of cancer research. Such recommendations will only come, however, with increased attention to the specifics of physical activity.

Our findings contribute to the broader research base accumulating around physical activity and cancer, by identifying preliminary attributes of physical activity (e.g., aerobic activity, ratio of time spent in an activity type, etc) that could be pursued further in future research. Our findings also demonstrate the potential importance of further examining the associations between physical activity and prostate cancer incidence, to determine whether ours and others' findings around the potential increased risk of prostate cancer in highly active men maintains significance in larger trials. By further examining specific attributes of physical activity, future research studies can aim to provide targeted messages that can give specific, measureable recommendations for physical activity to the broader population.

References

1. De Pergola G, Silvestris F. Obesity as a major risk factor for cancer. *J Obes*. 2013. doi:10.1155/2013/291546.

2. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *J Natl Cancer Inst*. 2012;104:1-26. doi:10.1093/jnci/djs207.

3. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol*. 2011. doi:10.1038/nri3041.

4. Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. *Euro J Cancer*. 2010;46:2593-2604. doi:10.1016/j.ejca.2010.07.028.

5. Tucker JM, Welk GJ, Beyler NK. Physical activity in U.S. adults. Compliance with the Physical Activity Guidelines for Americans. *Am J Prev Med*. 2011;40(4):454-461. doi:10.1016/j.amepre.2010.12.016.

6. United States Government. Memorandum M-13-13. Open Data Policy – Managing Information as an Asset. May 9, 2013.

7. Wen CP, Wai JPM, Tsai MK, et al. Minimum amount of physical activity for reduced mortality and extendd life expectancy: a prospective cohort study. *Lancet*. 2011;378:1244-53. doi:10.1016/S0140-6736(11)60749-6.

8. French DP, Olander EK, Chisholm A, McSharry J. Which behavior change techniques are most effective at increasing older adults' self-efficacy and physical activity behavior? A systematic review. *Ann Behav Med*. 2014;48:225-234. doi:10.1007/s12160-014-9593-z.